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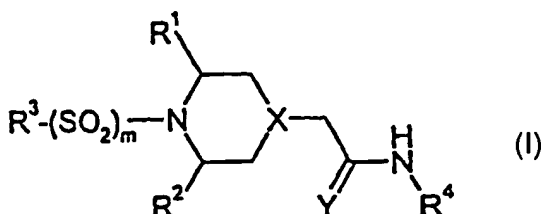
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(54) Title: NOVEL PIPERIDINE AND PIPERAZINE DERIVATIVES



(57) Abstract: The invention provides piperidine and piperazine derivatives of general formula (I), processes for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy.

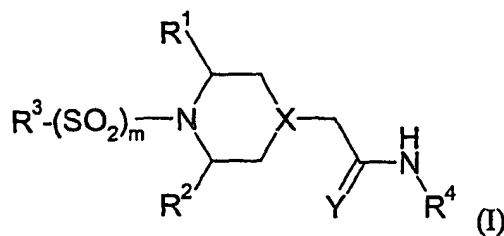
# Novel piperidine and piperazine derivatives

The present invention relates to piperidine and piperazine derivatives, processes for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy.

The P2X<sub>7</sub> receptor (previously known as P2Z receptor), which is a ligand-gated ion channel, is present on a variety of cell types, largely those known to be involved in the inflammatory/immune process, specifically, macrophages, mast cells and lymphocytes (T and B). Activation of the P2X<sub>7</sub> receptor by extracellular nucleotides, in particular adenosine triphosphate, leads to the release of interleukin-1 $\beta$  (IL-1 $\beta$ ) and giant cell formation (macrophages/microglial cells), degranulation (mast cells) and L-selectin shedding (lymphocytes). P2X<sub>7</sub> receptors are also located on antigen-presenting cells (APC), keratinocytes, salivary acinar cells (parotid cells), hepatocytes, erythrocytes, erythroleukaemic cells, monocytes, fibroblasts, bone marrow cells, neurones and renal mesangial cells.

It would be desirable to make compounds effective as P2X<sub>7</sub> receptor antagonists for use in the treatment of inflammatory, immune or cardiovascular diseases, in the aetiologies of which the P2X<sub>7</sub> receptor may play a role.

In accordance with the present invention, there is therefore provided a compound of general formula



wherein,

X represents a nitrogen atom or a group C(R<sup>5</sup>);

Y represents an oxygen or sulphur atom or a group  $\text{NR}^6$ , preferably an oxygen atom;  
either  $\text{R}^1$  and  $\text{R}^2$  each independently represent a hydrogen atom or a  $\text{C}_1\text{-C}_4$  alkyl  
group but do not both simultaneously represent a hydrogen atom, or  $\text{R}^1$  and  $\text{R}^2$  together  
represent a group  $-\text{CH}_2\text{ZCH}_2-$ ;

5        Z represents a bond, an oxygen or sulphur atom or a group  $\text{CH}_2$  or  $\text{NR}^7$ , and is  
preferably a bond;

m is 0 or 1;

$\text{R}^3$  represents a 5- to 10-membered unsaturated ring system which may comprise  
from 1 to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur,  
10        the ring system being optionally substituted by one or more substituents independently  
selected from halogen, nitro, cyano,  $\text{NR}^8\text{R}^9$ ,  $\text{C}_1\text{-C}_4$  alkyl- $\text{C}(\text{O})\text{NH}-$ ,  $\text{NHR}^{12}\text{C}(\text{O})-$ ,  
 $\text{C}_1\text{-C}_4$  alkyl- $\text{SO}_2-$ ,  $\text{C}_1\text{-C}_4$  alkyl- $\text{SO}_2\text{NH}-$ ,  $\text{C}_1\text{-C}_4$  alkyl- $\text{NHSO}_2-$ ,  $\text{C}_1\text{-C}_4$  alkoxy, and  
 $\text{C}_1\text{-C}_4$  alkyl optionally substituted by one or more fluorine atoms;

$\text{R}^4$  represents a phenyl or pyridinyl group, each of which is substituted in an ortho  
15        position with a substituent selected from halogen,  $\text{C}_1\text{-C}_4$  alkoxy,  $\text{C}_1\text{-C}_4$  alkylthio, and  
 $\text{C}_1\text{-C}_4$  alkyl optionally substituted by one or more fluorine atoms, the phenyl or pyridinyl  
group being optionally further substituted by one or more substituents independently  
selected from halogen, cyano, hydroxyl,  $\text{C}_1\text{-C}_4$  alkylthio,  $\text{C}_1\text{-C}_4$  alkyl- $\text{NH}-$ ,  
 $\text{NHR}^{13}\text{-C}_1\text{-C}_4$  alkyl-,  $\text{C}_1\text{-C}_4$  alkyl- $\text{SO}_2-$ ,  $\text{C}_1\text{-C}_4$  alkyl- $\text{SO}_2\text{NH}-$ ,  
20         $\text{C}_1\text{-C}_4$  alkyl- $\text{NHSO}_2-$ ,  $\text{C}_1\text{-C}_4$  alkyl- $\text{C}(\text{O})\text{NH}-$ ,  $\text{C}_1\text{-C}_4$  alkyl- $\text{NHC}(\text{O})-$ ,  $-\text{D-G}$ ,  
 $\text{C}_1\text{-C}_4$  alkoxy optionally substituted by  $-\text{NR}^{14}\text{R}^{15}$  or by  $\text{R}^{16}$ ; and  
 $\text{C}_1\text{-C}_4$  alkyl optionally substituted by one or more fluorine atoms or by one or more  
hydroxyl groups,

or  $\text{R}^4$  represents a 9- or 10-membered unsaturated bicyclic ring system which may  
25        comprise from 1 to 4 ring heteroatoms independently selected from nitrogen, oxygen and  
sulphur, the bicyclic ring system being optionally substituted by one or more substituents  
independently selected from halogen, oxo,  $\text{C}_1\text{-C}_4$  alkyl,  $\text{C}_1\text{-C}_4$  alkoxy,  $\text{C}_1\text{-C}_4$  alkylthio  
and  $-\text{NR}^{10}\text{R}^{11}$ ;

D represents an oxygen atom or a group  $(\text{CH}_2)_n$  or  $\text{CH}_2\text{NH}$ ;

30        n is 1, 2 or 3;

G represents a piperazinyl, morpholinyl or 2,5-diazabicyclo[2.2.1]heptyl group, or  
G represents a piperidinyl group optionally substituted by amino (-NH<sub>2</sub>);

R<sup>5</sup> represents a hydrogen atom, or a hydroxyl or C<sub>1</sub>-C<sub>4</sub> alkoxy group;

R<sup>6</sup> represents a hydrogen atom, or a cyano, nitro, hydroxyl, C<sub>1</sub>-C<sub>4</sub> alkyl or  
5 C<sub>1</sub>-C<sub>4</sub> alkoxy group;  
R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> each independently represent a hydrogen atom or a C<sub>1</sub>-C<sub>4</sub> alkyl group;  
R<sup>10</sup> and R<sup>11</sup> each independently represent a hydrogen atom or a C<sub>1</sub>-C<sub>4</sub> alkyl group,  
or R<sup>10</sup> and R<sup>11</sup> together with the nitrogen atom to which they are attached form a 5- or 6-  
membered saturated heterocyclic ring comprising one or two ring nitrogen atoms;

10 R<sup>12</sup> represents a hydrogen atom, or a C<sub>1</sub>-C<sub>4</sub> alkyl group optionally substituted by  
amino (-NH<sub>2</sub>);

R<sup>13</sup> represents a hydrogen atom, or a C<sub>1</sub>-C<sub>4</sub> alkyl group optionally substituted by  
hydroxyl;

R<sup>14</sup> and R<sup>15</sup> each independently represent a hydrogen atom or a C<sub>1</sub>-C<sub>4</sub> alkyl group  
15 optionally substituted by hydroxyl, or R<sup>14</sup> and R<sup>15</sup> together with the nitrogen atom to  
which they are attached form a 5- or 6-membered saturated heterocyclic ring comprising  
one or two ring nitrogen atoms; and

R<sup>16</sup> represents a 1-(C<sub>1</sub>-C<sub>4</sub>-alkyl)-piperidinyl group;

with the proviso that when m is 0, X is N and Y is O, then R<sup>4</sup> does not represent  
20 2-benzothiazolyl;  
or a pharmaceutically acceptable salt or solvate thereof.

In the context of the present specification, unless otherwise indicated, an alkyl  
substituent or alkyl moiety in a substituent group may be linear or branched. In the present  
25 invention, an alkyl group or moiety may contain up to 4 carbon atoms, for example,  
methyl, ethyl, propyl, isopropyl, butyl, isobutyl and t-butyl.

When the substituent group is NHR<sup>13</sup>-C<sub>1</sub>-C<sub>4</sub> alkyl-, it should be appreciated that the  
NHR<sup>13</sup> moiety may be attached to a terminal or internal carbon atom of the alkyl moiety  
30 and when the substituent group is alkoxy substituted by -NR<sup>14</sup>R<sup>15</sup>, the alkoxy group will

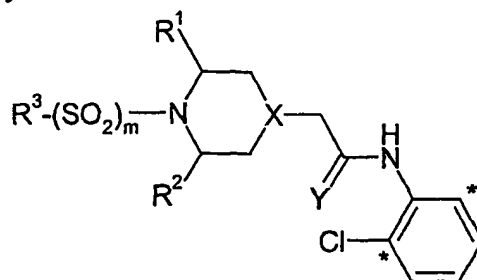
contain at least 2 carbon atoms and the group  $-NR^{14}R^{15}$  is not attached to the same carbon atom to which the oxygen atom is attached.

$R^3$  represents a 5- to 10-membered unsaturated ring system which may comprise 1, 2, 3 or 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted by one or more (i.e. at least one), e.g. one, two or three, substituents independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine), nitro, cyano,  $NR^8R^9$ ,  $C_1$ - $C_4$  alkyl- $C(O)NH$ - (e.g.  $CH_3C(O)NH$ -),  $NHR^{12}C(O)$ - (e.g.  $NH_2C(O)$ -,  $NH(CH_3)C(O)$ -,  $(CH_3)_2NC(O)$ -,  $NH_2CH_2CH_2NHC(O)$ -),  $C_1$ - $C_4$  alkyl- $SO_2$ - (e.g.  $CH_3SO_2$ -),  $C_1$ - $C_4$  alkyl- $SO_2NH$ - (e.g.  $CH_3SO_2NH$ -),  $C_1$ - $C_4$  alkyl- $NHSO_2$ - (e.g.  $CH_3NHSO_2$ -),  $C_1$ - $C_4$ , preferably  $C_1$ - $C_2$ , alkoxy, and  $C_1$ - $C_4$ , preferably  $C_1$ - $C_2$ , alkyl optionally substituted by one or more (i.e. at least one), e.g. one, two, three or four, fluorine atoms (e.g. trifluoromethyl). Specific substituents that may be mentioned include: methyl, amino ( $-NH_2$ ), cyano, methoxy, chloro, nitro,  $NH_2C(O)$ -,  $CH_3C(O)NH$ -,  $CH_3SO_2$ -,  $CH_3SO_2NH$ - and  $NH_2CH_2CH_2NHC(O)$ -.

The ring system may be monocyclic or polycyclic. If polycyclic, e.g. bicyclic, the two rings may be fused to one another or may be joined by a bond. If the ring system is bicyclic, it is preferred that the rings are fused to one another. Examples of ring systems that may be used include phenyl, pyridinyl, pyrimidinyl, naphthyl, furanyl, pyrrol, thienyl, isothiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, pyrazinyl, quinolinyl, isoquinolinyl, benzofuranyl, isobenzofuranyl, benzothienyl, pyrazolyl, indolyl, isoindolyl, purinyl, oxazolyl, isoxazolyl, thiazolyl, triazinyl, benzothiazolyl, benzooxazolyl, imidazopyrazinyl, triazolopyrazinyl, naphthyridinyl, furopyridinyl, thiopyranopyrimidinyl, pyridazinyl, quinazolinyl, pteridinyl, triazolopyrimidinyl, triazolopyrazinyl, thiapurinyl, oxapurinyl, deazapurinyl, thiazolopyrimidinyl, indolinyl, benzooxadiazolyl, benzothiadiazolyl, tetrahydroisoquiniliny, 2-(isoxazol-3-yl)thienyl, and thienopyrimidinyl. Preferred ring systems are phenyl, thienopyrimidinyl, purinyl, pyrimidinyl, thiazolopyrimidinyl, quinazolinyl, benzooxadiazolyl, benzothiadiazolyl,

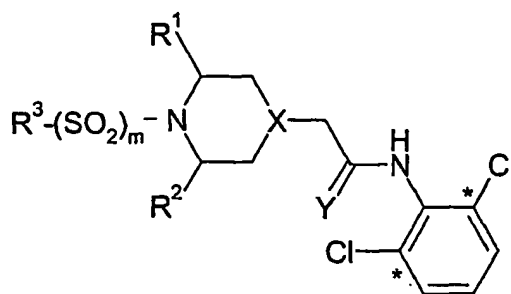
thienyl, imidazolyl, tetrahydroisoquiniliny, isoquinoliny, pyrazolyl, isoxazolyl, 2-(isoxazol-3-yl)thienyl and pyridinyl.

$R^4$  may represent a phenyl or pyridinyl group comprising at least one substituent  
 5 selected from halogen (e.g. fluorine, chlorine, bromine or iodine),  $C_1$ - $C_4$ , preferably  $C_1$ - $C_2$ , alkoxy,  $C_1$ - $C_4$ , preferably  $C_1$ - $C_2$ , alkylthio or  $C_1$ - $C_4$ , preferably  $C_1$ - $C_2$ , alkyl optionally substituted by one or more (i.e. at least one) fluorine atoms (e.g. trifluoromethyl), which substituent is attached to the phenyl or pyridinyl group at a position ortho (\*) with respect to the point of attachment of  $R^4$  to the rest of the molecule,  
 10 for example as illustrated below. Examples of preferred ortho substituents include chloro, methyl and trifluoromethyl.

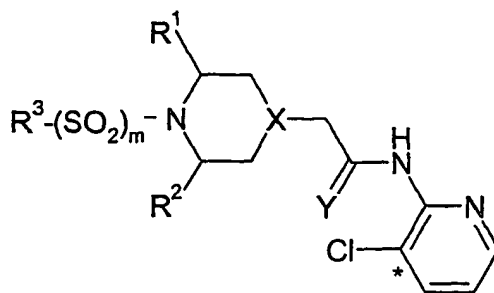


or

15



or



The phenyl or pyridinyl group may be optionally further substituted by one or more (i.e. at least one) (e.g. one, two, three or four) substituents independently selected from  
 5 halogen (e.g. fluorine, chlorine, bromine or iodine), cyano, hydroxyl, C<sub>1</sub>-C<sub>4</sub> alkylthio (e.g. methylthio or ethylthio), C<sub>1</sub>-C<sub>4</sub> alkyl-NH- (e.g. methylamino or ethylamino), NHR<sup>13</sup>-C<sub>1</sub>-C<sub>4</sub> alkyl-, C<sub>1</sub>-C<sub>4</sub>, preferably C<sub>1</sub>-C<sub>2</sub>, alkyl-SO<sub>2</sub>-, C<sub>1</sub>-C<sub>4</sub>, preferably C<sub>1</sub>-C<sub>2</sub>, alkyl-SO<sub>2</sub>NH-, C<sub>1</sub>-C<sub>4</sub>, preferably C<sub>1</sub>-C<sub>2</sub>, alkyl-NHSO<sub>2</sub>-, C<sub>1</sub>-C<sub>4</sub>, preferably C<sub>1</sub>-C<sub>2</sub>, alkyl-C(O)NH-, C<sub>1</sub>-C<sub>4</sub>, preferably C<sub>1</sub>-C<sub>2</sub>, alkyl-NHC(O)-, -D-G, C<sub>1</sub>-C<sub>4</sub> alkoxy  
 10 optionally substituted by -NR<sup>14</sup>R<sup>15</sup> or by R<sup>16</sup>, and C<sub>1</sub>-C<sub>4</sub>, preferably C<sub>1</sub>-C<sub>2</sub>, alkyl optionally substituted by one or more (i.e. at least one) fluorine atoms (e.g. trifluoromethyl) or by one or more (i.e. at least one) hydroxyl groups (e.g. hydroxymethyl).

Alternatively, R<sup>4</sup> may represent a 9- or 10-membered unsaturated fused bicyclic ring  
 15 system which may comprise 1, 2, 3 or 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted by one or more (i.e. at least one) (e.g. one, two, three or four) substituents independently selected from halogen (e.g. fluorine, chlorine, bromine or iodine), oxo, C<sub>1</sub>-C<sub>4</sub>, preferably C<sub>1</sub>-C<sub>2</sub>, alkyl, C<sub>1</sub>-C<sub>4</sub>, preferably C<sub>1</sub>-C<sub>2</sub>, alkoxy, C<sub>1</sub>-C<sub>4</sub>, preferably C<sub>1</sub>-C<sub>2</sub>, alkylthio and NR<sup>10</sup>R<sup>11</sup>.  
 20 Examples of suitable bicyclic ring systems include naphthyl, benzimidazolyl, quinolinyl, indolinyl, isoquinolinyl, benzofuranyl, isobenzofuranyl, benzothienyl, indolyl, isoindolyl, benzthiazolyl, benzoxazolyl and quinazolinyl. An example of an unsaturated fused bicyclic ring system substituted by an oxo group is oxindolyl.

D represents an oxygen atom or a group  $(CH_2)_n$  or  $CH_2NH$  (in that orientation), where n is 1, 2 or 3.

G represents a piperazinyl, morpholinyl or 2,5-diazabicyclo[2.2.1]heptyl group, or  
5 G represents a piperidinyl group optionally substituted by at least one amino group (e.g. 1-piperidinyl, 4-piperidinyl, 1-piperazinyl, 1-morpholinyl or 4-amino-1-piperidinyl).

$R^5$  represents a hydrogen atom, or a hydroxyl or  $C_1$ - $C_4$  alkoxy group. In a preferred embodiment,  $R^5$  represents a hydrogen atom.

10

$R^6$  represents a hydrogen atom, or a cyano, nitro, hydroxyl,  $C_1$ - $C_4$ , preferably  $C_1$ - $C_2$ , alkyl or  $C_1$ - $C_4$ , preferably  $C_1$ - $C_2$ , alkoxy group.

$R^7$ ,  $R^8$  and  $R^9$  each independently represent a hydrogen atom or a  $C_1$ - $C_4$ , preferably  
15  $C_1$ - $C_2$ , alkyl group.

$R^{10}$  and  $R^{11}$  each independently represent a hydrogen atom or a  $C_1$ - $C_4$ , preferably  $C_1$ - $C_2$ , alkyl group, or  $R^{10}$  and  $R^{11}$  together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated heterocyclic ring comprising one or two ring  
20 nitrogen atoms (e.g. pyrrolidinyl, piperidinyl or piperazinyl).

$R^{12}$  represents a hydrogen atom, or a  $C_1$ - $C_4$ , preferably  $C_1$ - $C_2$ , alkyl group optionally substituted by at least one amino group ( $-NH_2$ ).

25  $R^{13}$  represents a hydrogen atom, or a  $C_1$ - $C_4$ , preferably  $C_1$ - $C_2$ , alkyl group optionally substituted by at least one hydroxyl group.

$R^{14}$  and  $R^{15}$  each independently represent a hydrogen atom or a  $C_1$ - $C_4$ , preferably  $C_1$ - $C_2$ , alkyl group optionally substituted by at least one hydroxyl group, or  $R^{14}$  and  $R^{15}$   
30 together with the nitrogen atom to which they are attached form a 5- or 6-membered



saturated heterocyclic ring comprising one or two ring nitrogen atoms (e.g. pyrrolidinyl, piperidinyl or piperazinyl).

$R^{16}$  represents a 1-(C<sub>1</sub>-C<sub>4</sub>-alkyl)-piperidinyl group, e.g. 1-methylpiperidinyl,  
5 specifically 1-methylpiperidin-3-yl.

Preferred compounds of the invention include:

(+)-N-(2,6-Dimethylphenyl)-2-(3-methyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)acetamide,

10 *cis*-[2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)]-N-(2,6-dimethylphenyl)acetamide,

(+)-2-[3-Methyl-4-(4-methylphenyl)piperazin-1-yl]-N-(2,6-dimethylphenyl)acetamide,

15 *cis*-N-[3-Hydroxymethyl-2-methylphenyl]-2-(3,5-dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)acetamide,

(R)-2-[4-(1-Methylimidazol-4-sulphonyl-4-yl)-3-ethylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide,

*cis*-2-[3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl]-N-(2-methylphenyl)acetamide,

20 *cis*-N-(2-Chlorophenyl)-2-[3,5-dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl]acetamide,

*cis*-N-(2-Chlorophenyl)-2-[3,5-dimethyl-4-(9-methyl-9H-purin-6-yl)piperazin-1-yl]acetamide,

25 *cis*-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(isoquinolin-5-yl)acetamide,

*cis*-2-(3,5-Dimethyl-4-thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(quinolin-5-yl)acetamide,

*cis*-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(2-methyl-5-methylsulphonamidophenyl)acetamide,

*cis*-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(2-trifluoromethylphenyl)acetamide,

*cis*-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(3-methylpyridin-2-yl)acetamide,

5 *cis*-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(isoquinolin-1-yl)acetamide,

*cis*-4-(4-Amino-5-cyanopyrimidin-2-yl)-3,5-dimethylpiperazin-1-yl)-N-(2-chlorophenyl)acetamide,

*cis*-2-(4-Benzenesulphonyl-3,5-dimethylpiperazin-1-yl)-N-(2-chloro-phenyl)acetamide,

(+)-N-(2,6-Dimethylphenyl)-2-[(3-methyl-4-thiazolo(5,4-*d*)pyrimidin-7-yl)piperazin-1-yl]acetamide,

*cis*-N-(2-Chlorophenyl)-2-[(3,5-dimethyl-4-quinazolin-4-yl)piperazin-1-yl]acetamide,

15 N-(2-Chlorophenyl)-2-[(8-(thieno[2,3-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

N-(2-Methylphenyl)-2-[8-(9-methyl-9H-purin-6-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

20 2-[8-(9-Methyl-9H-purin-6-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(quinolin-5-yl)acetamide,

N-(Quinolin-5-yl)-2-[8-thiazolo[5,4-*d*]pyrimidin-7-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

N-(2-Methylphenyl)-2-[(8-thiazolo[5,4-*d*]pyrimidin-7-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

25 N-(2-Methyl-5-(methylsulphonyl)amidophenyl)-2-[8-(9-methyl-9H-purin-6-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

N-[2-Methyl-5-(methylsulphonyl)amidophenyl]-2-[(8-thiazolo[5,4-*d*]pyrimidin-7-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

30 N-[2-Methyl-5-(methylsulphonyl)amidophenyl]-2-[4-(thieno[2,3-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

*cis*-2-(3,5-Dimethyl-4-(thieno[2,3-d]pyrimidin-4-yl)piperazin-1-yl)-N-(2-methyl-5-(1-piperazinylmethyl)phenyl)acetamide, hydrochloride salt,

N-(2-Methylphenyl)-2-[(8-(thieno[2,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

5 N-[5-(Methanesulphonylamido-2-methylphenyl)-2-[8-(thieno[2,3-d]pyrimidin-4-yl)-8-azabicyclo[3.2.1]oct-3-yl]acetamide,

N-(2-Methyl-5-(1-piperazinylmethyl)phenyl)-2-[(8-(thieno[2,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

*cis*-N-(5-(2-Aminoethoxy)-2-methyl-phenyl)-2-(3,5-dimethyl-4-(thieno[2,3-d]pyrimidin-4-yl)piperazin-1-yl)acetamide, hydrochloride salt,

*cis*-N-(5-(2-(N-Methylamino)ethoxy)-2-methyl-phenyl)-2-(3,5-dimethyl-4-(thieno[2,3-d]pyrimidin-4-yl)piperazin-1-yl)acetamide, hydrochloride salt,

*cis*-N-(5-(2-(N-Methylamino)ethoxy)-2-methyl-phenyl)-2-(4-benzenesulphonyl)-3,5-dimethylpiperazin-1-yl)acetamide,

15 *cis*-N-[5-(2-Aminoethoxy)-2-methyl-phenyl)-2-(4-benzenesulphonyl-3,5-dimethyl)piperazin-1-yl]acetamide, hydrochloride salt,

N-(2-Oxo-2,3-dihydro-1H-indol-4-yl)-2-(8-thieno[2,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl)acetamide

N-(3-Fluoro-2-methyl-phenyl)-2-((8-quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl)acetamide,

20 N-(2-Methylphenyl)-2-[8-(benzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

N-(3-Fluoro-2-methylphenyl)-2-[8-(benzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

25 *cis*-N-(3-Fluoro-2-methyl-phenyl)-2-(4-benzenesulphonyl)-3,5-dimethylpiperazin-1-yl)acetamide,

N-(2-Methylphenyl)-2-[8-(3-cyanobenzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

30 2-[8-(3-Methoxybenzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide,

2-[8-(Benzo[1,2,5]oxadiazole-4-sulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide,

2-[8-(Benzo[1,2,5]thiadiazole-4-sulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide,

5 2-[8-(5-Chlorothiemo-2-yl)sulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide,

2-[8-(2-Chlorobenzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide,

10 2-[8-(5-Chloro-2-methoxybenzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide,

2-[8-(4-Acetylaminoethoxybenzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide,

N-(2-Methylphenyl)-2-[(8-(3-methylthieno[2,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

15 *cis*-2-(3,5-Dimethyl-4-(thieno[2,3-d]pyrimidin-4-yl)piperazin-1-yl)-N-(1-methyl-1H-benzoimidazol-2-yl)acetamide,

*cis*-2-(3,5-Dimethyl-4-(thieno[2,3-d]pyrimidin-4-yl)piperazin-1-yl)-N-(2-methyl-5-(4-piperidinylloxy)phenyl)acetamide, hydrochloride salt,

20 *cis*-2-(3,5-Dimethyl-4-benzenesulphonyl)piperazin-1-yl)-N-(2-methyl-5-(4-piperidinylloxy)phenyl)acetamide,

*cis*-2-(3,5-Dimethyl-4-(quinazolin-4-yl)piperazin-1-yl)-N-(2-methyl-5-(4-piperidinylloxy)phenyl)acetamide,

*cis*-2-(3,5-Dimethyl-4-(4-quinazolinyl)piperazin-1-yl)-N-(2-methyl-5-(piperazin-4-yl-methyl)phenyl)acetamide,

25 *cis*-2-(3,5-Dimethyl-4-(4-quinazolinyl)piperazin-1-yl)-N-(2-methyl-5-(2-(N-methylamino)ethoxy)phenyl)acetamide,

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide,

30 *cis*-N-(2-Methylphenyl)-2-[4-(3-nitrobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-acetamide,

*cis*-2-[4-(3-Aminobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide,

*cis*-2-(3,5-Dimethyl-4-(3-cyanobenzenesulphonyl)piperazin-1-yl)-N-(quinolin-5-yl)acetamide,

5 *cis*-2-(3,5-Dimethyl-4-(4-cyanobenzenesulphonyl)piperazin-1-yl)-N-(quinolin-5-yl)acetamide,

*cis*-2-(4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl)-N-(3-fluoro-2-methylphenyl)acetamide,

10 *cis*-2-(4-(4-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl)-N-(3-fluoro-2-methylphenyl)acetamide,

*cis*-2-[4-(3-Acetylaminobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide,

*cis*-2-[4-(3-Aminocarbonylbenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide,

15 *cis*-2-[4-(3-Methanesulphonylaminobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide,

*cis*-2-[4-(2-Methanesulphonylbenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(3-methoxy-2-methylphenyl)acetamide,

20 *cis*-2-[4-(2-Methanesulphonylbenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(3-fluoro-2-methylphenyl)acetamide,

*cis*-2-[4-(1-Methylimidazol-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide,

*cis*-2-[4-(1-Methylimidazol-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-(3-methoxy-2-methylphenyl)acetamide,

25 *cis*-2-[4-(1-Methylimidazol-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-(3-fluoro-2-methylphenyl)acetamide,

*cis*-2-[4-(3-Methanesulphonylbenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-trifluoromethylphenyl)acetamide,

30 *cis*-2-[4-(2-Aminoethylaminocarbonylbenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide,

*cis*-2-[4-(1,1,2,2-Tetrahydroisoquinilin-7-sulphonyl-7-yl)-3,5-dimethylpiperazin-1-yl]-N-(2,6-dimethylphenyl)acetamide,

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2,6-dimethylphenyl)acetamide,

5 *cis*-2-[4-(4-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide,

*cis*-2-[4-(2-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2,6-dimethylphenyl)acetamide, hydrochloride salt,

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-chlorophenyl)acetamide,

10 2-[8-(Isquinolin-1-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide,

*cis*-2-[4-(4-Acetamidobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide,

15 *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-trifluoromethylphenyl)acetamide,

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-methanesulphonamidophenyl)acetamide,

2-[8-(4-Benzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide,

20 2-[8-(2-Benzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide,

*cis*-2-[4-(1,2-Dimethylimidazol-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide,

25 *cis*-2-[4-(5-Chloro-1,3-dimethylpyrazole-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-(3-methoxy-2-methylphenyl)acetamide,

2-[8-(2-(Isoxazol-3-yl)thiophen-5-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide,

30 2-[8-(1,1,2,2-Tetrahydroisoquinilin-7-sulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide,

*cis*-2-[4-(5-Chloro-1,3-dimethylpyrazole-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide,

*cis*-2-[4-(3,5-Dimethylisoxazole-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide,

5 *cis*-2-[4-(2-Methanesulphonylbenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide,

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(3-methoxy-2-methylphenyl)acetamide,

10 *cis*-2-[4-(4-Methanesulphonylbenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide,

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(5-cyano-2-methylphenyl)acetamide,

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(5-acetamido-2-methylphenyl)acetamide,

15 (R)-2-[4-(4-Cyanobenzenesulphonyl)-3-methylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide,

(S)-2-[4-(4-Cyanobenzenesulphonyl)-3-methylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide,

20 *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-methanesulphonylphenyl)acetamide,

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-(4-amino-1-piperidinyl)methyl)phenyl]acetamide,

(R)-2-[4-(4-Methanesulphonylbenzenesulphonyl)-3-methylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide,

25 (R)-2-[4-(4-Acetamidobenzenesulphonyl)-3-methylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide,

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-(1-piperazinylmethyl)phenyl)acetamide,

30 *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-(4-piperidinylamino)methyl)phenyl]acetamide,

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-(1-morpholinyl)methyl)phenyl)acetamide,

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-(2-hydroxyethylamino)methyl)phenyl)acetamide,

5 *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-(S,S)-(2,5-diazabicyclo[2.2.1]hept-2-yl)methyl)phenyl)acetamide,

(R)-2-[4-(2-Pyridinesulphonyl)-3-methylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide,

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-3-(4-amino-1-piperidinyl)methyl)phenyl)acetamide,

10 *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-3-(4-piperidinylamino)methyl)phenyl)acetamide,

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-3-(1-piperazinylmethyl)phenyl)acetamide,

15 *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-3-(S,S)-(2,5-diazabicyclo[2.2.1]hept-2-yl)methyl)phenyl)acetamide,

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-3-(1-morpholinyl)methyl)phenyl)acetamide,

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-3-(2-(1-pyrrolidinyl)ethoxy)phenyl)acetamide,

20 (±) *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-3-(1-methylpiperidin-3-yl)methoxy)phenyl)acetamide,

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-4-(2-(1-pyrrolidinyl)ethoxy)phenyl)acetamide,

25 (±) *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-4-(1-methylpiperidin-3-yl)methoxy)phenyl)acetamide,

(±) *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-5-(1-methylpiperidin-3-yl)methoxy)phenyl)acetamide,

(±) *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-6-(1-methylpiperidin-3-yl)methoxy)phenyl)acetamide, and

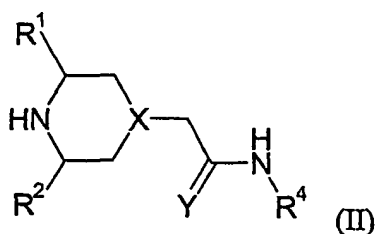
30 *cis*-2-[4-(1-Methylimidazol-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-((2-



methyl-3-(2-(1-pyrrolidinyl)ethoxy)phenyl)acetamide,  
and their pharmaceutically acceptable salts and solvates.

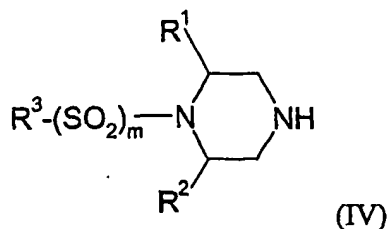
The present invention further provides a process for the preparation of a compound  
5 of formula (I) as defined above which comprises:

(a) reacting a compound of general formula

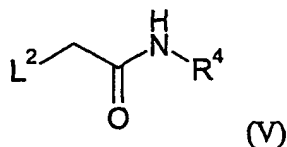


wherein X, Y, R<sup>1</sup>, R<sup>2</sup> and R<sup>4</sup> are as defined in formula (I), with a compound of general  
10 formula (III), R<sup>3</sup>-(SO<sub>2</sub>)<sub>m</sub>-L<sup>1</sup>, wherein L<sup>1</sup> represents a leaving group (e.g. a halogen atom  
or triflate) and m and R<sup>3</sup> are as defined in formula (I); or

(b) when X represents a nitrogen atom and Y represents an oxygen atom, reacting a  
compound of general formula

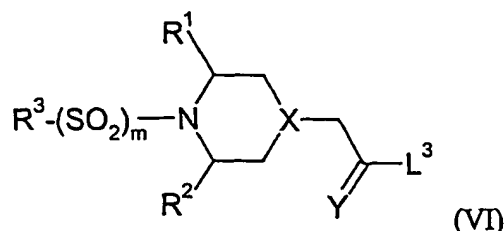


15 wherein m, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined in formula (I), with a compound of general  
formula



wherein L<sup>2</sup> represents a leaving group such as a halogen atom and R<sup>4</sup> is as defined in  
20 formula (I); or

(c) reacting a compound of general formula



wherein  $L^3$  represents a leaving group such as a halogen atom or hydroxyl group and  $m$ ,  $X$ ,  $Y$ ,  $R^1$ ,  $R^2$  and  $R^3$  are as defined in formula (I), with a compound of general formula (VII),  
 5  $H_2N - R^4$ , wherein  $R^4$  is as defined in formula (I);

and optionally after (a), (b) or (c) converting the compound of formula (I) obtained to a pharmaceutically acceptable salt or solvate thereof.

10 Processes (a) and (b) are conveniently carried out in the presence of a base, e.g. a metal carbonate such as potassium or caesium carbonate or a trialkylamine such as triethylamine, preferably *N,N*-diisopropylethylamine, and in the presence of a polar solvent (e.g. 1-methyl-2-pyrrolidinone, dimethylformamide, ethanol, tetrahydrofuran or 1,4-dioxane).

15 Process (c) is conveniently carried out in the presence of a base and a polar solvent as described above for processes (a) and (b). In addition, a coupling reagent is suitably used, for example, 1,1'-carbonyldiimidazole, 1,3-dicyclohexylcarbodiimide or bromo-tris-oxy-tripyrrolidinophosphonium hexafluorophosphate.

20 Compounds of formulae (II), (III), (IV), (V), (VI) and (VII) are either commercially available, are well known in the literature or may be prepared easily using known techniques.

25 It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl, carboxyl or amino groups in the

starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve at a certain stage the removal of one or more protecting groups.

5       The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

10       It will be appreciated that certain compounds of formula (I) may be converted to further compounds of formula (I) by techniques known in the art such as alkylation, hydrolysis, amide bond formation, esterification or reductive amination.

15       The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate, or an alkali metal salt such as a sodium or potassium salt.

20       Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

25       The compounds of the present invention are advantageous in that they possess pharmacological activity and have utility as modulators of P2X<sub>7</sub> receptor activity. They are therefore indicated as pharmaceuticals for use in the treatment or prevention of rheumatoid arthritis, osteoarthritis, psoriasis, allergic dermatitis, asthma, hyperresponsiveness of the airway, chronic obstructive pulmonary disease (COPD),  
30    bronchitis, septic shock, glomerulonephritis, irritable bowel disease, Crohn's disease,

ulcerative colitis, atherosclerosis, growth and metastases of malignant cells, myoblastic leukaemia, diabetes, neurodegenerative disease, Alzheimer's disease, meningitis, osteoporosis, burn injury, ischaemic heart disease, stroke, peripheral vascular disease and varicose veins.

5

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

10

In another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

15

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

20

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

25

The invention further provides a method of effecting immunosuppression (e.g. in the treatment of rheumatoid arthritis, irritable bowel disease, atherosclerosis, psoriasis, pulmonary disease, e.g. COPD or bronchitis, or diseases of the central nervous system, e.g. Alzheimer's disease or stroke) which comprises administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined to a patient.

30

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disease or condition indicated. For effecting immunosuppression, the daily dosage of the compound of formula (I) will typically be in the range from 0.001 mg/kg to 30 mg/kg.

The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.10 to 70 %w, of active ingredient, and, from 1 to 99.95 %w, more preferably from 30 to 99.90 %w, of a pharmaceutically acceptable adjuvant, diluent or carrier, all percentages by weight being based on total composition.

Thus, the present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

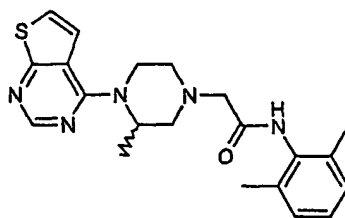
The pharmaceutical composition of the invention may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by

parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally.

The present invention will now be further explained by reference to the following  
5 illustrative examples.

### Example 1

(+)-N-(2,6-Dimethylphenyl)-2-(3-methyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)acetamide



10

i) (+)-1,1-Dimethylethyl, 3-methyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazine-1-carboxylate

A solution of 4-chloro-thieno[2,3-*d*]pyrimidine (0.2g) and (+)-1,1-dimethylethyl, 3-methylpiperazine-1-carboxylate (J. Med. Chem., 1993, 36, 690-698) (0.23g) in ethanol  
15 (50ml) was heated under reflux for 24 hours. The solvent was evaporated and the residue purified by flash column chromatography eluting with ethyl acetate/*iso*hexane (3:7) to give the subtitle compound as a yellow gum. Yield 0.33g.

MS: APCI(+ve) 335 (M+1,100%)

20

ii) (+)-2-Methyl-1-(thieno[2,3-*d*]pyrimidine-4-yl)piperazine, trifluoroacetic acid salt

A mixture of the product from step (i) (0.33g) and trifluoroacetic acid (4 ml) in dichloromethane (5 ml) was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure. Toluene (20 ml) was added to the residue and then  
25 evaporated under reduced pressure to give the crude subtitle compound as a gum. The product was used without further purification in the next step.

MS: APCI(+ve) 235 (M+1,100%)

iii) (+)-N-(2,6-Dimethylphenyl)-2-(3-methyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)acetamide

A mixture of the product from step (ii) (0.23g), N,N-diisopropylethylamine (0.65g) and 2-chloro-N-(2,6-dimethylphenyl)acetamide (0.2g) in dimethylformamide (4ml) was heated at 80°C for 18 hours. The reaction mixture was cooled and diluted with ethyl acetate. The organic solution was washed with a small volume of water and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography eluting with ethyl acetate/*isohexane* (6:4) to give the product as a gum. The gum was further purified by reverse phase high pressure liquid chromatography (methanol / 0.1% aqueous ammonium acetate, gradient elution 15% to 85% organic phase) to give the title product, after freeze drying, as a beige solid. Yield 0.095g.

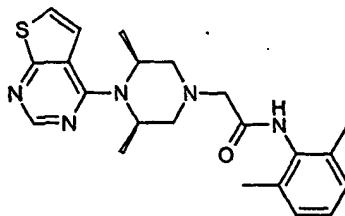
MS: APCI(+ve) 396 (M+1,100%)

<sup>1</sup>H NMR:  $\delta$  (CDCl<sub>3</sub>) 8.5(2H, s); 7.32(2H, q); 7.13(3H, m); 4.98(1H, bs); 4.60(1H, bd); 3.59(1H, dt); 3.25(2H, q); 3.12(1H, bd); 2.98(1H, d); 2.72(1H, dd); 2.55(1H, dt); 2.28(6H, s); 1.53(3H, d).

MP: 184-185 °C

**Example 2**

*cis*-[2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)]-N-(2,6-dimethylphenyl)acetamide



**i) *cis*-1,1-Dimethylethyl, 3,5-dimethyl-4-(thieno[2,3-*d*]pyrimidine-4-yl)piperazin-1-carboxylate**

A solution of 4-chloro-thieno[2,3-*d*]pyrimidine (4.0g), *cis*-1,1-dimethylethyl, 3,5-dimethylpiperazine-1-carboxylate (J. Med. Chem., 1999, 4(7), 1123-1114) (12g) and  
5 N,N-diisopropylethylamine (10ml) in 1-methyl-2-pyrrolidinone (30ml) was heated at 120 °C for 5 days under nitrogen. The reaction mixture was cooled and diluted with ethyl acetate. The organic solution was washed with water, dried (MgSO<sub>4</sub>) and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with ethyl acetate/*iso*hexane (2:8) to give the subtitle compound as  
10 a beige solid. Yield 5.5g.

MS: APCI(+ve) 349 (M+1,100%)

**ii) *cis*-2,6-Dimethyl-1-(thieno[2,3-*d*]pyrimidin-4-yl)piperazine, trifluoroacetic acid salt**

15 The subtitle compound was prepared from the product of step (i) (0.15g) by the method of Example 1 step (ii) as a gum. This was used without purification in the next step.

MS: APCI(+ve) 249 (M+1,100%).

**20 iii) *cis*-[2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)]-N-(2,6-dimethylphenyl)acetamide**

A mixture of the product from step (ii), N,N-diisopropylethylamine (0.37ml) and 2-chloro-N-(2,6-dimethylphenyl)acetamide (0.08g) in 1-methyl-2-pyrrolidinone (5ml) was heated at 100°C for 24 hours. The reaction mixture was cooled and diluted with ethyl acetate. The  
25 organic solution was washed with a small volume of water, dried (MgSO<sub>4</sub>) and the solvent evaporated under reduced pressure. The residual red oil was purified by reverse phase high pressure liquid chromatography (acetonitrile / 0.1% aqueous ammonium acetate, gradient elution 20% to 80% organic phase) to give the title product, after freeze drying, as a cream solid. Yield 0.05g.



MS: APCI(+ve) 410 (M+1,100%)

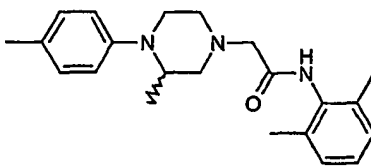
<sup>1</sup>H NMR: δ (CDCl<sub>3</sub>) 8.5(2H, s); 7.38(1H, d); 7.26(1H, d); 7.14(3H, m); 5.10(2H, bs); 3.29(2H, s); 3.01(2H, d); 2.65(2H, dd); 2.30(6H, s); 1.56(6H, d).

MP: 186-189 °C

5

### Example 3

(+)-2-[3-Methyl-4-(4-methylphenyl)piperazin-1-yl]-N-(2,6-dimethylphenyl) acetamide



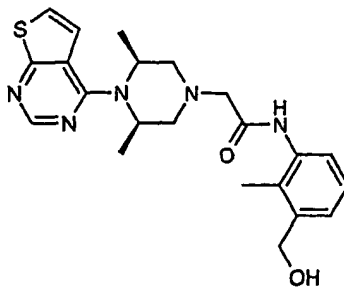
The title compound was prepared from (+)-3-methyl-4-(4-methylphenyl)piperazine (0.1 g) and 2-chloro-N-(2,6-dimethylphenyl)acetamide (0.1 g) by the method of Example 1  
10 step (iii) as a white solid. Yield 0.056g.

MS: APCI(+ve) 352 (M+1,100%).

<sup>1</sup>H NMR: δ (CDCl<sub>3</sub>) 8.63(1H, s); 7.09(5H, m); 6.87(2H, d); 3.78(1H, bm); 3.24(2H, d);  
15 3.17(2H, m); 2.95(1H, m); 2.88(1H, dd); 2.72(2H, m); 2.29(3H, s); 2.26(6H, s); 1.08(3H, d).

### Example 4

*cis*-N-[3-Hydroxymethyl-2-methylphenyl]-2-(3,5-dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)acetamide  
20



i) *cis*-N-[3-((1,1-Dimethyl)-1-dimethylethyl)silyloxymethyl-2-methylphenyl]-2-(3,5-dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)acetamide

The subtitle compound was prepared from N-(3-((1,1-dimethyl-1-dimethylethyl)silyloxymethyl)-2-methylphenyl)-2-chloroacetamide (Chem. Abs., 1997, 765311) (0.1g) and the product from Example 2 step (ii) (0.1g) by the method of Example 2 step (iii) as a red oil. This was used directly in the next step without further purification.

5

**ii) *cis*-N-[3-Hydroxymethyl-2-methylphenyl]-2-(3,5-dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)acetamide**

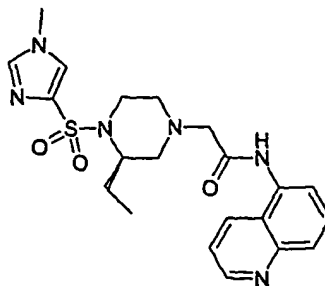
The subtitle product from step (i) (0.15g) in anhydrous tetrahydrofuran was treated with a 1M solution of tetrabutyl ammonium fluoride in tetrahydrofuran (0.31ml) and the mixture  
10 stirred at room temperature for 1 hour. The solvent was removed under reduced pressure and the residue purified by high pressure liquid chromatography (acetonitrile / 0.1% aqueous ammonium acetate, gradient elution 20% to 80% organic phase) to give the title compound as a white solid. Yield 0.025g.

15 **MS:** APCI(+ve) 426 (M+1,100%)

**<sup>1</sup>H NMR:**  $\delta$  (CDCl<sub>3</sub>/DMSO) 8.97(1H,s), 8.49(1H,s), 7.89(1H,d), 7.32(1H, d), 7.26(3H, m), 5.09(2H, bs), 4.74(2H, s), 3.27(2H, s), 2.96(2H, d), 2.63(2H, dd), 2.36(3H, s), 1.58(6H, bs)  
**MP:** 203-204°C

20 **Example 5**

**(R)-2-[4-(1-Methylimidazol-4-sulphonyl-4-yl)-3-ethylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide**



**i) (R)-3-Ethyl-1-(phenylmethyl)-2,5-piperazinedione**

To a stirred solution of (R)-N-BOC-2-aminobutyric acid (3.36g) and ethyl N-benzylglycine (4.52g) in dichloromethane (50ml) at 15 °C was added dicyclohexylcarbodiimide (3.59g). The temperature was maintained at 10-15 °C for a further 2h and then allowed to stir at ambient temperature for a further 16h. The mixture was filtered and the mother liquor  
5 collected and solvent evaporated under reduced pressure. The residue was re-dissolved in dichloromethane (20ml) and hydrogen chloride gas passed through the mixture for 20 minutes. The mixture was quenched with aq. saturated sodium bicarbonate solution and extracted with ethyl acetate, collected, dried (MgSO<sub>4</sub>) and solvent evaporated under reduced pressure to leave a colourless oil. This was purified by crystallisation from  
10 ether/iso-hexane mixtures to give the subtitle compound as a white solid. Yield: 1.35g

<sup>1</sup>H NMR δ (DMSO) 8.30(s, 1H), 7.24-7.39(m, 5H), 4.60(d, 1H), 4.44(d, 1H), 3.92(t, 1H), 3.78(d, 3H), 1.75(m, 2H), 0.84(t, 3H)

15 **ii) (R)-3-Ethyl-1-phenylmethylpiperazine**

A stirred solution of the product from step (i) (6.0g) in tetrahydrofuran (250ml) at 0 °C was treated with lithium aluminium hydride (3.44g). The mixture was allowed to stir at ambient temperature for 24h and then set at reflux for 4h. The mixture was carefully quenched with 10% aq. sodium hydroxide solution (10ml). After stirring for 30 minutes the mixture was  
20 filtered and the mother liquor partitioned between ethyl acetate and brine. The organic layer collected, dried (MgSO<sub>4</sub>) and solvent evaporated under reduced pressure to give the subtitle compound as a pale yellow oil. Yield: 5.8g

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 7.32(s, 5H), 3.50(dd, 2H), 2.62-3.0(m, 5H), 2.00(m, 1H), 1.70(t, 1H),  
25 1.57(s, 1H), 1.27(m, 2H), 0.90(t, 3H)

**iii) (R)-1-(1-Methylimidazol-4-sulphonyl-4-yl)-2-ethyl-4-phenylmethylpiperazine**

The subtitle compound was prepared from the product of step (ii) (0.5g) and 1-methylimidazole-4-sulphonyl chloride (0.5g) by the method of Example 80 step (i) as a  
30 pale yellow solid. Yield: 0.53g

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 7.46(s, 1H), 7.38(s, 1H), 7.29(m, 5H), 3.80(s, 2H), 3.47(d, 1H), 3.3(d+m, 2H), 2.64(d, 2H), 2.08(m, 2H), 1.79(m, 2H), 0.82(t, 3H)

5 **iv) (R)-1-(1-Methylimidazol-4-sulphonyl-4-yl)-2-ethylpiperazine**

The subtitle compound was prepared from the product of step (iii) (0.49g) by the method of Example 80 step (ii) as a pale yellow solid. Yield: 0.32g

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 7.6(d, 2H), 7.5(m, 4H), 4.05(s, 1H), 3.73(s, 3H), 3.42(d, 1H), 3.04(d, 2H), 2.87(m, 1H), 2.32(m, 1H), 1.87(m, 2H), 0.91(t, 3H)

**v) (R)-2-[4-(1-Methylimidazol-4-sulphonyl-4-yl)-3-ethylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide**

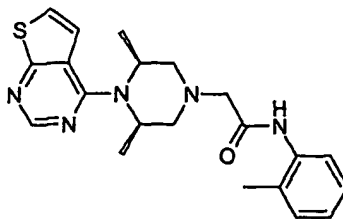
The title compound was prepared from the product of step (iv) (0.23g) and 2-chloro-N-(quinolin-5-yl)acetamide (0.21g) (J. Indian Chem Soc, 1940, 17, 619-621) by the method of Example 80 step (iii) as a cream solid. Yield: 21mg

MS: APCI (+ve) 443 (M+1)

<sup>1</sup>H NMR δ (CD<sub>3</sub>OD) 9.16(d, 1H), 9.07(d, 1H), 8.10(s, 3H), 7.97(t, 1H), 7.81(d, 1H), 7.70(t, 1H), 7.50(dd, 1H), 4.29(m, 2H), 4.10(m, 2H), 3.81(s, 3H), 3.69(m, 2H), 3.32(m, 2H), 3.15(m, 2H), 1.84(m, 2H), 0.99(t, 3H)

**Example 6**

**cis-2-[3,5-Dimethyl-4-(thieno[2,3-d]pyrimidin-4-yl)piperazin-1-yl]-N-(2-methylphenyl)acetamide**



The title compound was prepared from the product of Example 9 step (ii) (0.316g) and 2-methylaniline (0.09g) by the method of Example 8 step (v) as a white solid.

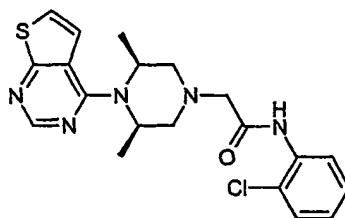
Yield 0.202g

5 MS: APCI(+ve) 396 (M+1, 100%)

<sup>1</sup>H NMR: δ (DMSO) 9.25(1H, s), 8.40(1H, d), 7.60-7.67(3H,m), 7.26(2H, m),  
7.10(1H, m), 5.01(2H, bs), 3.23(2H, s), 2.96(2H, d), 2.45(2H, m), 2.29(3H, s), 1.50(6H, m)  
MP: 174-175 °C

#### 10 Example 7

*cis*-N-(2-Chlorophenyl)-2-[3,5-dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl]acetamide



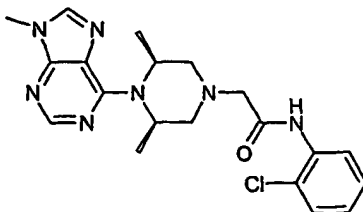
The title compound was prepared from the product of Example 8 step (ii) (0.316g) and  
15 2-chloroaniline (0.107g) by the method of Example 1 step (iii) as a white solid.  
Yield 0.119g.

MS: APCI(+ve) 416(M+1, 100%)

<sup>1</sup>H NMR: δ(DMSO) 9.70(1H, s), 8.55(1H, d), 7.27-7.42(3H, m), 7.26(2H, s), 7.08(1H, t),  
20 5.08(2H, bs), 3.26(2H, s), 2.94(2H, d), 2.60(2H, m), 1.63(6H, d)  
MP: 206-207 °C

#### Example 8

*cis*-N-(2-Chlorophenyl)-2-[3,5-dimethyl-4-(9-methyl-9H-purin-6-yl)piperazin-1-yl]acetamide  
25



**i) *cis*-1,1-Dimethylethyl, 3,5-dimethyl-4-(9-methyl-9H-purin-6-yl)piperazine-1-carboxylate**

The subtitle compound was prepared from 6-chloro-9-methyl-9H-purine (J. Org. Chem.,  
1983, 48(6), 850-5) (2g) and *cis*-1,1-dimethylethyl, 3,5-dimethylpiperazine-1-carboxylate  
5 (2.74g) by the method of Example 2 step (i) as beige solid. Yield 0.2g.

$^1\text{H}$  NMR:  $\delta$  ( $\text{CDCl}_3$ ) 8.40(1H, S), 7.73(1H, S), 4.20-4.00(3H, BRM),  
3.30-3.00(3H, BRM), 1.5(9H, S), 1.40(6H, D)

10

**ii) *cis*-2,6-Dimethyl-1-(9-methyl-9H-purin-6-yl)piperazine, trifluoroacetic acid salt**

The subtitle compound was prepared from the product of step (i) (0.2g) by the method of  
Example 1 step (ii) as a red gum. This was used directly in the next step.

15 MS: APCI(+ve) 247 (M+1, 100%)

**iii) *cis*-1,1-Dimethylethyl, 2-(3,5-dimethyl-4-(9-methyl-9H-purin-6-yl)piperazin-1-yl)acetate**

A mixture of the product from step (ii) (0.34g), *tert*-butyl bromoacetate (0.13g) and sodium  
20 bicarbonate (0.8g) in acetone was heated at 45°C for 18 hours. The reaction mixture was  
filtered and the filtrate evaporated under reduced pressure. The residual brown gum was  
purified by flash chromatography eluting with ethyl acetate/*iso*hexane/ triethylamine  
(7:2.5:0.5) to give the subtitle compound as a pale yellow gum. Yield 0.12g.

25 MS: APCI(+ve) 361(M+1, 100%)

**iv) *cis*-2-(3,5-Dimethyl-4(9-methyl-9H-purin-6-yl)piperazin-1-yl)acetic acid, hydrochloride salt**

The product from step (iii) (0.12g) in dichloromethane was treated with 1M hydrogen chloride in diethyl ether (12 ml). The mixture was stirred at room temperature for 18 hours. The solvent was evaporated under reduced pressure to give the subtitle product as a pale yellow solid. Yield 0.15g.

MS: APCI(+ve) 305 (M+1, 100%)

**v) *cis*-N-(2-Chlorophenyl)-2-[3,5-dimethyl-4-(9-methyl-9H-purin-6-yl)piperazin-1-yl]acetamide**

Bromo-tris-oxy-tripyrrolidinophosphonium hexafluorophosphate (known as PyBroP) (0.18g) was added to a stirred solution of the product from step (iv) (0.14g), 2-chloroaniline (0.05g) and N,N-diisopropylethylamine (0.3g) in anhydrous dimethylformamide (6ml). After stirring for 4 hours a further aliquot of 2-chloroaniline (0.1ml) and PyBroP (0.18g) were added and the mixture further stirred at room temperature for four days. Water was added and the precipitate filtered to give the crude product as a brown solid (0.07g). This was purified by high pressure liquid chromatography (acetonitrile / 0.1% aqueous ammonium acetate, gradient elution 25% to 75% organic phase) to give the title product as a white solid. Yield 0.04g.

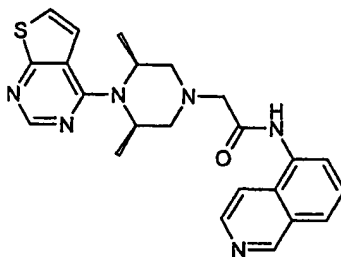
MS: APCI(+ve) 414/416 (M+1, 100%)

<sup>1</sup>H NMR: δ (CDCl<sub>3</sub>/DMSO) 9.76(1H, s), 8.52(1H, dd), 8.39(1H, s), 7.78(1H, s), 7.40(1H, dd), 7.31(1H, dt), 7.07(1H, dt), 5.50(2H, bs), 3.83(3H, s), 3.26(2H, s), 2.94(2H, d), 2.59(2H, m), 1.58(6H, d)

MP: 221-222 °C

**Example 9**

***cis*-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(isoquinolin-5-yl)acetamide**



**i) *cis*-1,1-Dimethylethyl, 2-(3,5-dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)acetate**

The subtitle compound was prepared from the product of Example 2 step (ii) (3.0g) and  
5 tert-butyl bromoacetate (1.15g) by the method of Example 8 step (iii) as a white solid.  
Yield 1.0g.

MS: APCI(+ve) 363 (M+1,100%)

**10 ii) *cis*-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)acetic acid, hydrochloride salt**

The product from step (i) (1.0g) in 1,4-dioxane was treated with 4M hydrogen chloride in  
1,4-dioxane (40 ml). The mixture was stirred at room temperature for 18 hours. The  
solvent was evaporated under reduced pressure to give the subtitle compound as a white  
15 solid. Yield 1.9g.

MS; APCI(+ve) 307 (M+1,100%)

**20 iii) *cis*-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(isoquinolin-5-yl)acetamide**

The title product was prepared from the product of step (ii) (0.2g) and 5-aminoisoquinoline  
(0.084g) by the method of Example 8 step (v) as a white solid. Yield 0.11g.

MS: APCI(+ve) 433 (M+1,100%)



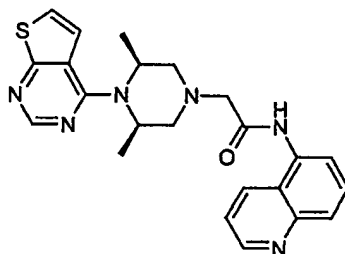
$^1\text{H}$  NMR:  $\delta$  ( $\text{CDCl}_3$ ) 9.62(1H,bs), 9.30(1H, s), 8.59(1H, d), 8.51(1H, s), 8.46(1H, d), 7.85(1H,d), 7.68(2H, m), 7.38(1H, d), 7.28(1H, m), 5.13(2H, bs), 3.38(2H, s), 3.03(2H, d), 2.70(2H, dd), 1.65(6H, d)

MP: 213-216 °C

5

### Example 10

*cis*-2-(3,5-Dimethyl-4-thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(quinolin-5-yl)acetamide



10 The title compound was prepared from the product of Example 9 step (ii) (0.207g) and 5-aminoquinoline (0.072g) by the method of Example 8 step (v) as a white solid.  
Yield 0.11g.

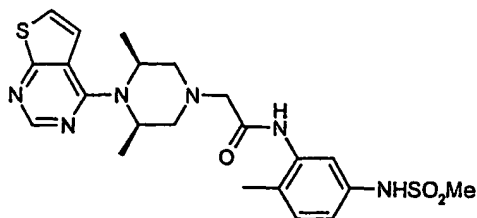
MS: APCI(+ve) 433 ( $M+1$ , 100%)

15  $^1\text{H}$  NMR:  $\delta$  ( $\text{CDCl}_3$ ) 9.53(1H,s), 8.97(1H, s), 8.51(1H,s), 8.28(1H,s), 8.00(1H, s), 7.77(1H,t), 7.47(1H, m), 7.42(1H,d), 7.37(1H, d), 5.13(2H,s), 3.38(2H,s), 3.03(2H,d), 2.71(2H,d), 2.29(3H,s), 1.63(6H,d)

MP: 194-195 °C

### 20 Example 11

*cis*-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(2-methyl-5-methylsulphonamidophenyl)acetamide



**i) 2-Methyl-5-bis(methylsulphonyl)amido-1-nitrobenzene**

To a mixture of 5-nitro-4-methylaniline (3.04g) and N,N-diisopropylethylamine (5.2ml) in dichloromethane (40ml) was added dropwise a solution of methanesulphonyl chloride (2.29g) in dichloromethane (10ml) over 40mins. After stirring for 16 hours the mixture was poured into 2% aq. HCl. The organic phase collected and further washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and solvent evaporated under reduced pressure to leave the crude product. This was purified by silica-gel chromatography eluting with dichloromethane to give the subtitle compound as a pale yellow solid. Yield 4.46g. This was used directly in the next step.

**ii) 2-Methyl-5-bis(methylsulphonyl)amido-1-aniline**

A mixture of the product from step (i) (3.8g), ammonium chloride (3.8g), reduced iron powder (3.8g) in ethanol (30ml) and water (10ml) were stirred at 80 °C for 5 minutes. The mixture was filtered through Celite and further washed with ethanol and dichloromethane. The filtrate was concentrated to a quarter of the volume and then water added to give a brown precipitate. This was filtered to give the subtitle compound as a brown solid. Yield 1.25g. The mother liquor was further partitioned between water and ethyl acetate. The organic phase collected, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to give a second batch of the subtitle compound as an orange solid. Yield 1.1g.

<sup>1</sup>H NMR: δ (DMSO) 6.98 (1H, d), 6.65 (1H, s), 6.56 (1H, d), 2.50 (6H, s), 2.06 (3H, s)

**iii) *cis*-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(2-methyl-5-bis(methylsulphonyl)amidophenyl)acetamide**

The subtitle product was prepared from the product of Example 9 step (ii) (0.318g) and the product of step (ii) (0.172g) by the method of Example 8 step (v) as a white solid. Yield 0.21g. This product was used directly in the next step without further purification.

iv) ***cis*-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(2-methyl-5-methylsulphonamidophenyl)acetamide**

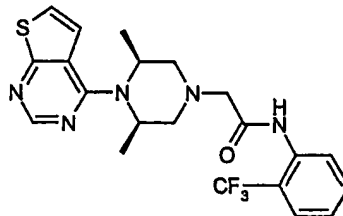
A mixture of the product from step (iii) (0.21g) and potassium carbonate (0.5g) was stirred in methanol (20ml) and water (10ml) over 24 hours at room temperature. The solid  
 5 product was filtered and purified by reverse phase HPLC to give the title compound as white solid. Yield 0.058g.

MS: APCI(+ve) 489(M+1, 100%)

<sup>1</sup>H NMR:  $\delta$  (DMSO) 9.66(1H,s), 9.23(1H,s), 8.40(1H,s), 7.60(3H,s), 7.17(1H,d),  
 10 6.94(1H,d), 4.50(2H,bs), 3.22(2H,s), 2.93(2H,s), 2.43(2H,m), 2.22(3H,s), 1.49(6H,d)

**Example 12**

***cis*-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(2-trifluoromethylphenyl)acetamide**



i) ***cis*-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)acetyl chloride, hydrochloride salt**

A mixture of the product from Example 9 step (ii) (1.15g) and oxalyl chloride (1.2ml) in dichloromethane (100 ml) was treated with 2 drops of dimethylformamide. After 24 hours  
 20 at room temperature a further aliquot of oxalyl chloride (3.6ml) was added and the mixture heated under reflux for 48 hours. The solvent was evaporated under reduced pressure. Toluene was added to the residue and then evaporated under reduced pressure to give the subtitle product as a yellow oil (0.95g).

25 MS: (methanol added to give the methyl ester) :APCI(+ve) 320 (M(methyl ester)+1, 100%)

ii) *cis*-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(2-trifluoromethylphenyl)acetamide

A mixture of the product from step (i) (0.2g), 2-trifluoromethylaniline (0.11g) and N,N-diisopropylethylamine in 1,4-dioxane (5ml) was heated at 80°C for 18 hours. LC mass  
5 spectrum analysis showed *cis*-(3,5-dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)acetic acid present. PyBroP (0.18g) and 4-dimethylaminopyridine (0.05g) were added and the mixture further stirred at room temperature for 18 hours. The solvent was evaporated under reduced pressure and the residue purified by high pressure liquid chromatography (acetonitrile / 0.1% aqueous ammonium acetate, gradient elution 25% to  
10 75% organic phase) to give the title product as a white solid. Yield 0.08g.

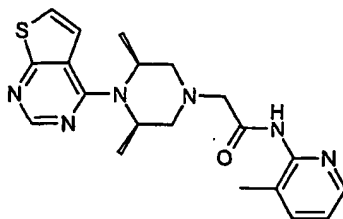
MS: APCI(+ve) 450 (M+1, 100%)

<sup>1</sup>H NMR:  $\delta$  (CDCl<sub>3</sub>) 9.41(1H, bs), 8.49(1H, s), 8.34(1H, d), 7.65(1H, d), 7.60(1H, t),  
7.37(1H, d), 7.27(2H, m), 5.06(2H, bs), 3.24(2H, s), 2.92(2H, d), 2.59(2H, dd), 1.55(6H, d)

15 MP: 154-155 °C

Example 13

*cis*-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(3-methylpyridin-2-yl)acetamide



20

The title compound was prepared by from the product of Example 12 step (i) (0.2g) and 2-amino-3-methylpyridine (0.076g) by the method of Example 12 step (ii) as a cream solid. Yield 0.025g.

25 MS: APCI(+ve) 397 (M+1, 100%)

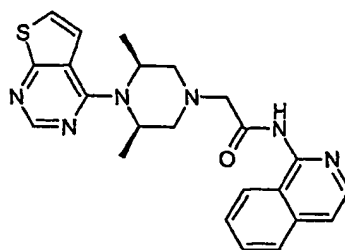
<sup>1</sup>H NMR:  $\delta$  (CDCl<sub>3</sub>) 9.13(1H, s), 8.47(1H, s), 8.31(1H, d), 7.60(1H, d), 7.40(1H, m), 7.27(1H, d), 7.13(1H, m), 5.09(2H, bs), 3.28(2H, s), 2.91(2H, d), 2.61(2H, m), 2.3(3H, s), 1.60(6H, d)

MP: 157-159 °C

5

#### Example 14

*cis*-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(isoquinolin-1-yl)acetamide



10 The title product was prepared by from the product of Example 12 step (i) (0.2g) and isoquinolin-1-ylamine (0.1g) by the method of Example 12 step (ii) as a cream solid. Yield 0.055g.

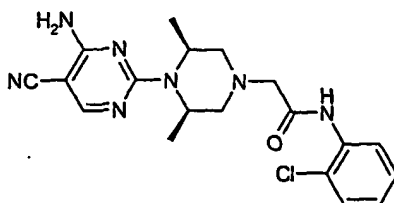
MS : APCI(+ve) 433 (M+1, 100%)

15 <sup>1</sup>H NMR:  $\delta$  (CDCl<sub>3</sub>) 9.65(1H, bs); 8.49(1H, s); 8.37(1H, bs); 8.05(1H, bd); 7.72(1H, t); 7.60(2H, t); 7.39(1H, d); 7.26(1H, m); 5.12(2H, bs); 3.39(2H, s); 3.07(2H, d); 2.67(2H, dd); 1.63(6H, d).

MP: 206-207 °C

#### 20 Example 15

*cis*-2-(4-(4-Amino-5-cyanopyrimidin-2-yl)-3,5-dimethyl-piperazin-1-yl)-N-(2-chlorophenyl)acetamide



**i) 2-Chloro-N-(2-chlorophenyl)acetamide**

2-Chloroaniline (5g) was dissolved in dichloromethane (100ml) and chloroacetyl chloride (3.11ml) and N,N-diisopropylethylamine (13.65ml) were added at 0 °C under a nitrogen atmosphere. The mixture was stirred for 1 hour at 0 °C and 12 hours at room temperature, then quenched with water. The product was extracted with dichloromethane. The organic layer was washed with water, brine, dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to leave the subtitle product as a beige solid. Yield 7.5g. This was used in the next step without further purification.

MS: ES(-ve) 203 (M-1, 100%)

**ii) *cis*-N-(2-Chlorophenyl)-2-(3,5-dimethylpiperazin-1-yl)acetamide**

The product of step (i) (5.9g) was dissolved in ethanol (50ml) and *cis*-2,6-dimethylpiperazine (3g) and sodium hydrogencarbonate (6.63g) were added at room temperature under a nitrogen atmosphere. The mixture was heated under reflux for 24 hours and the cooled solution was filtered and the filtrate was evaporated under reduced pressure. The residue was dissolved in 1M HCl (22ml) and washed with dichloromethane. The aqueous solution was then basified to pH13 with a solution of sodium hydroxide and the product was extracted with dichloromethane. The organic layer was washed with water, brine, collected, dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give the subtitle compound as a beige solid. Yield 4g.

MS: ES(+ve) 282(M+1,100%)

**iii) *cis*-2-(4-(4-Amino-5-cyanopyrimidin-2-yl)-3,5-dimethylpiperazin-1-yl)-N-(2-chlorophenyl)acetamide**

A mixture of the product from step (ii) (0.5g), 4-amino-2-chloro-5-cyanopyrimidine (0.275g) and N,N-diisopropylethylamine (1.55ml) in 1-methyl-2-pyrrolidinone (5ml) was heated under nitrogen at 120 °C for 3 days. The cooled mixture was partitioned between ethyl acetate and water. The organic phase collected was dried (MgSO<sub>4</sub>) and the solvent

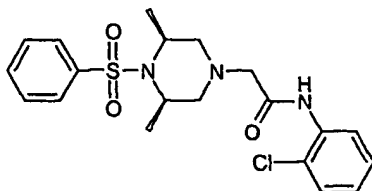
evaporated. The crude product purified by silica-gel chromatography eluting with 2% ethyl acetate in *isohexane* to give the title compound as white solid. Yield 0.1g.

MS: APCI (+ve) 400 (M+1, 100%)

5  $^1\text{H}$  NMR:  $\delta$  (DMSO) 9.67(1H, s), 8.32(1H, dd), 8.29(1H, s), 7.53(1H, dd), 7.37(1H, t), 7.23(2H, brs), 7.15(1H, t), 4.76-4.72(2H, m), 3.23(2H, s), 2.86(2H, d), 2.38(2H, dd), 1.36(6H, d)

### Example 16

10 *cis*-2-(4-Benzenesulphonyl-3,5-dimethylpiperazin-1-yl)-N-(2-chloro-phenyl)acetamide



Benzenesulphonyl chloride (0.124g) was added to a solution of the product from Example 15 step (ii) (0.2g) in pyridine (2ml). The mixture was stirred at room temperature for 16 hours and then the solvent was evaporated under reduced pressure. The residue was  
15 purified by flash silica-gel chromatography eluting with 1% EtOH, 1% Et<sub>3</sub>N, 98%CH<sub>2</sub>Cl<sub>2</sub> followed by trituration with ethyl acetate to give the title compound. Yield 0.03g.

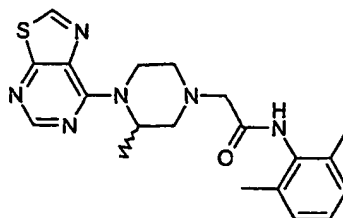
MS: APCI(+ve) 422 (M+1,100%)

20  $^1\text{H}$  NMR:  $\delta$  (CDCl<sub>3</sub>) 9.49 (brs, 1H), 8.48 (dd,1H), 7.82 (dd,2H), 7.60-7.50 (m,3H), 7.37 (dd,1H), 7.30 (m,1H), 7.05 (dt,1H), 4.17 (quin,2H), 3.07 (s,2H), 2.65 (d,2H), 2.15 (dd,2H), 1.55 (s,6H).

M.P: 182-3°C

### Example 17

25 (+)-N-(2,6-Dimethylphenyl)-2-[(3-methyl-4-thiazolo(5,4-*d*)pyrimidin-7-yl)piperazin-1-yl]acetamide



i) **(+)-N-(2,6-Dimethylphenyl)-2-(3-methylpiperazin-1-yl)acetamide**

The subtitle compound was prepared from 2-chloro-*N*-(2,6-dimethylphenyl)acetamide (7g) and (+)-2-methyl-piperazine (3.55g) by the method of Example 15 step (ii) as a white solid.

5 Yield 7g.

MS: ES(+ve) 262(M+1, 100%)

ii) **(+)-N-(2,6-Dimethylphenyl)-2-[(3-methyl-4-thiazolo(5,4-*d*)pyrimidin-7-yl)piperazin-1-yl]acetamide**

10

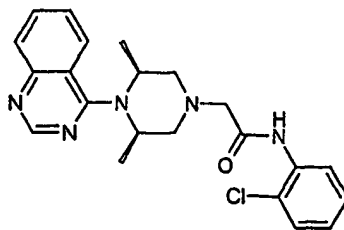
The title compound was prepared from the product of step (i) (0.381g) and 7-chloro-thiazolo[5,4,*d*]pyrimidine (Chem. Pharm. Bull. 1968, (16(4), 750-755) (0.25g) by the method of Example 15 step (iii) as a beige solid. Yield 0.01g.

15 MS: ES(+ve) 397(M+1, 100%)

<sup>1</sup>H NMR:  $\delta$  (CDCl<sub>3</sub>) 8.84(1H, s), 8.77(1H, s), 8.48(1H, s), 7.18-7.06(3H, m), 3.14(2H, s), 3.88-2.68(7H, brm), 2.26(6H, s), 1.25(3H, m)

**Example 18**

20 ***cis*-N-(2-Chlorophenyl)-2-[(3,5-dimethyl-4-quinazolin-4-yl)piperazin-1-yl]acetamide**



A mixture of the product from Example 15 step (ii) (2.1g), 4-chloroquinazoline (1.23g) (J. Chem. Soc., 1944, 619-623) and *N,N*-diisopropylethylamine (6.15ml) in 1-methyl-2-



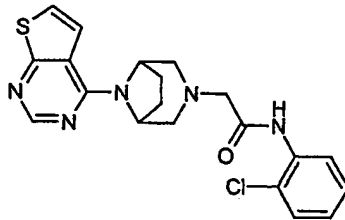
pyrrolidinone (14ml) under nitrogen was heated at 120 °C for 4 days. The cooled mixture was partitioned between ethyl acetate and water. The organic layer was further washed with water, brine, dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The residue was purified by silica-gel chromatography eluting with ethyl acetate/ isohexane (4:6) to  
 5 give the title compound as a white solid. Yield 0.08g.

MS: ES(+ve) 410(M+1,100%), ES(-ve) 408(M-1,100%)

<sup>1</sup>H NMR: δ (DMSO) 9.81(1H, s), 8.82(1H, brs), 8.30(1H, dd), 8.18(1H, d), 7.87(2H, d),  
 7.63-7.58(1H, m), 7.55(1H, dd), 7.38(1H, t), 7.17(1H, t), 4.38(2H, brs), 3.26(2H, s),  
 10 2.69(4H, brs), 1.30-1.15(6H, m)

#### Example 19

**N-(2-Chlorophenyl)-2-[(8-(thieno[2,3-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide**



15 **i) 1,1-Dimethylethyl, 3-[(2-chlorophenylcarbamoyl)methyl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate**

A mixture of 1,1-dimethylethyl, 3,8-diaza-bicyclo[3.2.1]octane-8-carboxylate (0.048g) (J. Med. Chem., 1998, 41(5), 674-681), sodium bicarbonate (0.058g), potassium iodide  
 20 (0.003g) and the product of Example 15 step (i) (0.051g) in ethanol (0.5ml) was heated at 70°C for 3 hours. The cooled mixture was partitioned between ethyl acetate and water and the organic phase was washed with water and brine, dried (MgSO<sub>4</sub>) and the solvent evaporated under reduced pressure. Purification was by flash silica-gel chromatography eluting with 2%EtOH, 1%Et<sub>3</sub>N, 97%CH<sub>2</sub>Cl<sub>2</sub>. Yield 0.068g.

25 MS: ES(+ve) 380 (M+1,100%)

**ii) N-(2-Chlorophenyl)-2-(3,8-diaza-bicyclo[3.2.1]oct-3-yl)acetamide trifluoroacetic acid salt**

The subtitle compound was prepared from the product of step (i) (0.068g) by the method of

5 Example 1 step (ii) as a white solid. Yield 0.061g.

MS: ES(+ve) 280 (M+1,100%)

**iii) N-(2-Chlorophenyl)-2-[(8-(thieno[2,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide**

The title compound was prepared from the product of step (ii) (0.061g) by the method of Example 15 step (iii), with heating for 1 hour only, as a white solid. Yield 0.04g.

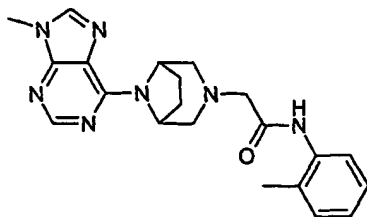
MS: APCI(+ve) 414 (M+1,100%)

15 <sup>1</sup>H NMR: δ (CDCl<sub>3</sub>) 9.65 (s,1H), 8.53 (dd,1H), 8.49 (s,1H), 7.41 (dd,1H), 7.33-7.28 (m,3H), 7.07 (t,1H), 5.02 (brs,1H), 3.18 (s,2H), 2.95 (d,2H), 2.77 (d,2H), 2.32 (m,2H), 2.12 (m,2H).

M.P: 164 °C

**20 Example 20**

**N-(2-Methylphenyl)-2-[8-(9-methyl-9H-purin-6-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide**



**i) 1,1-Dimethylethyl, 3-phenylmethyl-3,8-diazabicyclo[3.2.1]oct-8-carboxylate**

25 3-Phenylmethyl-3,8-diazabicyclo[3.2.1]octane hydrochloride salt (1.15g) was dissolved in dichloromethane (16ml) and water (16ml) and sodium hydrogencarbonate (1.61g) were

added. The mixture was stirred rapidly for 10 minutes at room temperature and then di-tert-butyl dicarbonate (1.15g) was added in portions. The mixture was stirred rapidly for an additional 2 hours. The organic layer was separated, dried over magnesium sulphate, filtered and concentrated to afford a white crystalline solid. Yield 1.45g.

5

MS: ES(+ve) 303 (M+1,100%)

**ii) 1,1-Dimethylethyl, 3,8-diazabicyclo[3.2.1]oct-8-carboxylate hydrochloride salt**

A solution of the product from step (i) (1.45g) was dissolved in ethyl acetate (12ml) and cooled at -10 °C under a nitrogen atmosphere. 1M HCl in diethyl ether (4.81ml) was added dropwise, causing the salt to precipitate out of solution. The mixture was stirred an additional 1 hour and the crystalline product was collected by filtration and dried in a vacuum oven. This white solid was dissolved in methanol (18ml) and 10% palladium on carbon (0.1g) added under a nitrogen atmosphere. The mixture was then stirred vigorously under an hydrogen atmosphere for 12 hours. After completion of the reaction, the mixture was filtered through Celite and the mother liquor concentrated to afford the subtitle compound as a white crystalline solid. Yield 1.18g.

15

<sup>1</sup>H NMR: δ (CDCl<sub>3</sub>) 4.34(2H, brs), 3.16(4H, brs), 2.27-2.09(4H, m), 1.47 (9H, s)

20

**iii) 1,1-Dimethylethyl, 3-[(2-methylphenylcarbamoyl)methyl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate**

A mixture of the product from step (ii) (0.16g), 2-chloro-N-(2-methyl)acetamide (Synthesis, 1982, (9), 795-796) (0.13g), sodium hydrogencarbonate (0.16g), and potassium iodide (8mg) in ethanol (2ml) under a nitrogen atmosphere was heated at 70 °C for 4 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water, brine, dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The residue was purified by silica-gel chromatography eluting with 2% ethanol/ 1% triethylamine in dichloromethane to give the subtitle compound as beige solid. Yield 0.23g.

30

MS: ES(+ve) 360 (M+1,100%)

**iv) N-(2-Methylphenyl)-2-[3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide, trifluoroacetic acid salt**

A mixture of the product from step (iii) (0.23g) in dichloromethane (30ml) and trifluoroacetic acid (1.80ml) under a nitrogen at room temperature was stirred for 24 hours. The mixture was concentrated under reduced pressure to leave brown gum. This was used in the next step without further purification.

MS: ES(+ve) 260 (M+1,100%)

**v) N-(2-Methylphenyl)-2-[8-(9-methyl-9H-purin-6-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide**

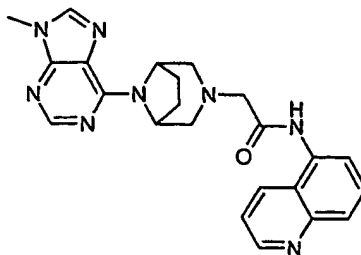
A mixture of the product from step (iv) (0.12g), 6-chloro-9-methylpurine (0.06g) (J. Org. Chem., 1983, 48(6), 850-855), and N,N-disopropylethylamine (1ml) in 1,4-dioxane (5ml) were heated together at reflux for 5 hours. The volatiles were removed under reduced pressure and the residue purified by reverse phase HPLC eluting with a gradient from 5% acetonitrile in aqueous 1% ammonium acetate to 75% over 7min. The title product was obtained, by freeze drying, as a white solid. Yield: 0.027g.

MS: APCI(+ve) 392 (M+1,100%)

<sup>1</sup>H NMR: δ (DMSO); 9.16(s, 1H), 8.27(s, 1H), 8.15(s, 1H), 7.75(d, 1H), 7.10(t, 1H), 7.08(t, 1H), 3.74(s, 3H), 5.70(bs, 1H), 5.00(bs, 1H), 3.74(s, 3H), 3.07(s, 2H), 2.90(m, 2H), 2.50-1.80(m, 6H), 2.30(s, 3H)

**Example 21**

**2-[8-(9-Methyl-9H-purin-6-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(quinolin-5-yl)acetamide**



**i) 1,1-Dimethylethyl, 3-[(quinolin-5-ylcarbamoyl)methyl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate**

The subtitle compound was prepared from the product of Example 20 step (ii) (0.24g) and  
 5 2-chloro-*N*-(quinolin-5-yl)acetamide (J. Indian Chem. Soc, 1940, 17, 619-621) (0.234g) by  
 the method of Example 20 step (iii) as a pale yellow solid. Yield 0.38g.

MS: ES(+ve) 397 (M+1,100%)

**10 ii) 2-(3,8-Diazabicyclo[3.2.1]oct-3-yl)-*N*-(quinolin-5-yl)acetamide, trifluoroacetic acid salt**

The subtitle compound was prepared from the product of step (i) (0.38g) by the method  
 Example 20 step of step (iv) as a pale yellow gum. This was used directly in the next step.

15 MS: ES(+ve) 297 (M+1,100%)

**iii) 2-[8-(9-Methyl-9H-purin-6-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-*N*-(quinolin-5-yl)acetamide**

A mixture of the product from step (ii) (0.20g), 6-chloro-9-methylpurine (0.1g) (J. Org.  
 20 Chem., 1983, 48(6), 850-855), and *N,N*-disopropylethylamine (1ml) in 1,4-dioxane (5ml)  
 were heated together at reflux for 4 hours. The volatiles were removed under reduced  
 pressure and the residue purified by reverse phase HPLC eluting with a gradient from 5%  
 acetonitrile in aqueous 1% ammonium acetate to 75% over 7min. The title product was  
 obtained, by freeze drying, as a white solid. Yield: 0.047g.

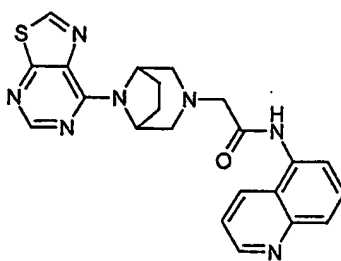
25

MS: APCI(+ve) 429(M+100%), APCI(-ve) 427(M-1,100%)

<sup>1</sup>H NMR: δ (DMSO); 9.9(bs, 1H), 8.90(m, 1H), 8.40(d, 1H), 8.30(s, 1H), 8.18(s, 1H), 7.90(d, 1H), 7.80(d, 1H), 7.75(t, 1H), 7.60(m, 1H), 5.78(bs, 1H), 5.00(bs, 1H), 3.78(s, 3H), 3.30(s, 2H), 2.90(m, 2H), 2.70-1.80(m, 6H).

5 **Example 22**

**N-(Quinolin-5-yl)-2-[8-thiazolo[5,4-*d*]pyrimidin-7-yl]-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide**



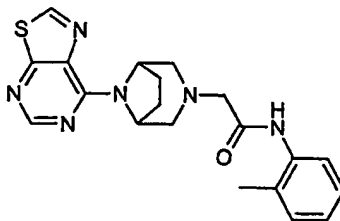
The title compound was prepared from the product Example 21 step (ii) (0.1g) and  
10 7-chlorothiazolo[5,4-*d*]pyrimidine (Chem. Pharm. Bull, 1968, 16(4), 750-755) (0.06g) by the method of Example 21 step (iii) as a pale yellow solid. Yield 0.1g.

MS: ES(+ve) 432 (M+1, 100%)

<sup>1</sup>H NMR: δ (CDCl<sub>3</sub>) 9.62(1H, s), 8.99-8.98(1H, m), 8.77(1H, s), 8.50(1H, s), 8.26(1H, d),  
15 8.16(1H, d), 7.99(1H, d), 7.75(1H, t), 7.52-7.49(1H, m), 6.04(1H, brs), 5.29(1H, brs), 3.27(2H, s), 3.03(2H, d), 2.83(2H, brs), 2.22(2H, brs), 1.70(1H, brs), 1.45(1H, dd)

**Example 23**

**N-(2-Methylphenyl)-2-[(8-thiazolo[5,4-*d*]pyrimidin-7-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide**



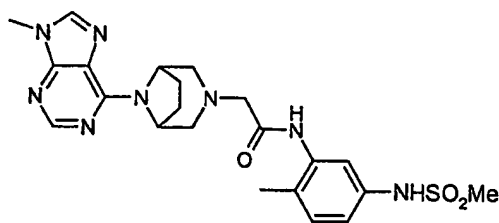
The title compound was prepared from the product of Example 20 step (iv) (0.1g) and 7-chlorothiazolo[5,4-*d*]pyrimidine (Chem. Pharm. Bull, 1968, 16(4), 750-755) (0.06g) by the method of Example 21 step (iii) as a white solid. Yield 0.06g.

5 MS: ES(+ve) 395 (M+1, 100%)

<sup>1</sup>H NMR: δ (CDCl<sub>3</sub>) 8.99(1H, s), 8.75(1H, s), 8.48(1H, s), 8.08(1H, d), 7.27-7.21(2H, m), 7.08(1H, t), 6.00(1H, brs), 5.29(1H, brs), 3.15(2H, s), 2.95(2H, d), 2.74(2H, brs), 2.38(3H, s), 2.27-2.07(4H, m)

#### 10 Example 24

**N-(2-Methyl-5-(methylsulphonyl)amidophenyl)-2-[8-(9-methyl-9H-purin-6-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide**



#### i) 2-Chloro-N-(5-bis(methylsulphonyl)amido-2-methylphenyl)acetamide

15 A mixture of the product from step (ii) (0.62g) and N,N-diisopropylethylamine (1.04ml) in dichloromethane (40ml) at 10 °C was treated with chloroacetyl chloride (0.19ml) dropwise. After stirring for 4 hours the mixture was poured into saturated sodium bicarbonate solution and the organic phase collected and further washed with brine, collected, dried (CaCl<sub>2</sub>) and solvent evaporated under reduced pressure to leave a yellow gum. This was  
20 purified by silica-gel chromatography eluting with 10% diethyl ether in dichloromethane to give the subtitle product as a white solid. Yield 0.71g.

MS: APCI (-ve) 353 (M-1, 100%)

25 ii) 1,1-Dimethylethyl, 3-[(5-bis(methylsulphonyl)amido-2-methylphenylcarbamoyl)methyl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

The subtitle compound was prepared from the product of step (i) (0.266g) and the product from Example 20 step (ii) (0.2g) by the method of Example 20 step (iii) as a white solid.

Yield 0.45g.

5 MS: ES(+ve) 531 (M+1,100%)

**iii) 2-(3,8-Diazabicyclo[3.2.1]oct-3-yl)-N-[5-bis(methylsulphonyl)amido-2-methylphenyl]acetamide, trifluoroacetic acid salt**

The subtitle compound was prepared from the product of step (ii) (0.45g) by the method of  
10 Example 20 step (iv) as a white solid. Yield 0.42g.

MS: ES(+ve) 431 (M+1,100%)

**iv) N-[5-Bis(methylsulphonyl)amido-2-methylphenyl]-2-[8-(9-methyl-9H-purin-6-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide**  
15

The subtitle compound was prepared from the product of step (iii) (0.2g) and 6-chloro-9-methylpurine (J. Org. Chem., 1983, 48(6), 850-855) (0.1g) by the method of Example 20 step (v) as white solid. Yield 0.1g.

20 MS: ES(+ve) 563 (M+1,100%)

**v) N-(2-Methyl-5-(methylsulphonyl)amidophenyl)-2-[8-(9-methyl-9H-purin-6-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide**

A mixture of the product from step (iv) (0.1g) and sodium bicarbonate (0.05g) in wet  
25 ethanol (2ml) was heated at reflux for 1.5 hours, cooled and filtered. Purification was by flash silica-gel chromatography eluting with 2.5% EtOH, 1%aq. NH<sub>3</sub>, 96.5% CH<sub>2</sub>Cl<sub>2</sub> followed by trituration with ethyl acetate to give the title product as a white solid. Yield 0.066g.

30 MS: AP(+ve) 485 (M+1,100%)



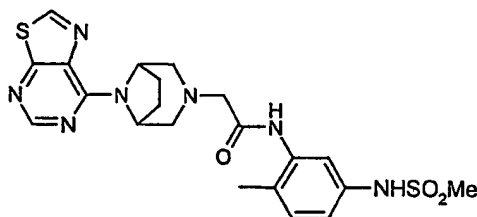
<sup>1</sup>H NMR:  $\delta$  (CDCl<sub>3</sub>): 9.19 (s,1H), 8.40 (s,1H), 8.14 (d,1H), 7.74 (s,1H), 7.20 (d,1H), 7.12 (dd,1H), 7.08 (s,1H), 3.84 (s,3H), 3.17 (s,2H), 2.97 (s,3H), 2.90 (d,2H), 2.75 (d,2H), 2.37 (s,3H), 2.15 (brn, 4H).

M.P: 216-217°C

5

### Example 25

**N-[2-Methyl-5-(methylsulphonyl)amidophenyl]-2-[(8-thiazolo[5,4-d]pyrimidin-7-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide**



- 10 **i) N-[5-Bis(methylsulphonyl)amido-2-methylphenyl]-2-[(8-thiazolo[5,4-d]pyrimidin-7-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide**

The subtitle compound was prepared from the product of Example 24 step (iii) (0.21g) and 7-chloro-thiazolo[5,4-d]pyrimidine (Chem. Pharm. Bull, 1968, 16(4), 750-755) (0.069g) by the method of Example 20 step (v) as a white solid. Yield 0.113g.

15

MS: APCI(+ve) 566 (M+1,100%)

- ii) N-[2-Methyl-5-(methylsulphonyl)amidophenyl]-2-[(8-thiazolo[5,4-d]pyrimidin-7-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide**

- 20 The title compound was prepared from the product of step (i) (0.113g) by the method of Example 24 step (v) as a white solid. Yield 0.085g.

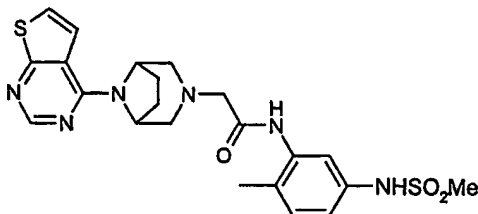
MS: APCI(+ve) 488 (M+1,100%)

- <sup>1</sup>H NMR:  $\delta$  (CDCl<sub>3</sub>) 9.18 (s,1H), 8.76 (s,1H), 8.48 (s,1H), 8.17 (d,1H), 7.31 (s,1H), 7.20 (d,1H), 7.13 (dd,1H), 3.21 (s,2H), 2.95 (s,3H), 2.92 (m,2H), 2.76 (m,2H), 2.38 (s,3H), 2.17(br m, 4H).
- 25

MP: 145-187 °C

### Example 26

N-[2-Methyl-5-(methylsulphonyl)amidophenyl]-2-[4-(thieno[2,3-*d*]pyrimidin-4-yl)-  
3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide



i) N-[(5-Bis(methylsulphonyl)amido-2-methylphenyl)-2-[4-(thieno[2,3-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide

The subtitle compound was prepared from the product of Example 24 step (iii) (0.216g) and 4-chlorothieno[2,3-*d*]pyrimidine (0.056g) by the method of Example 20 step (v) as a white solid. Yield 0.13g.

MS: ESI (+ve) 565 (M+1, 100%)

ii) N-[2-Methyl-5-(methylsulphonyl)amidophenyl]-2-[4-(thieno[2,3-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide

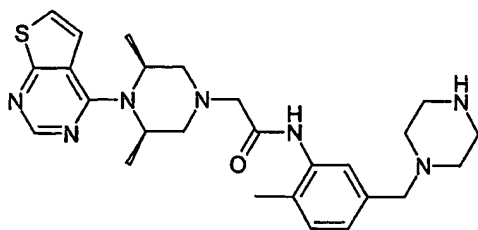
The title compound was prepared from the product of step (i) (0.130g) by the method of Example 24 step (v) as a white solid. Yield 0.025g.

MS: APCI(+ve) 487 (M+1, 100%)

<sup>1</sup>H NMR: δ (DMSO) 9.18(1H, s), 8.38(1H, s), 7.71-7.62(3H, m), 7.17(1H, d), 6.93(1H, dd), 5.04(2H, brs), 3.12(2H, s), 2.93(3H, s), 2.90(2H, d), 2.58(2H, d), 2.23(3H, s), 2.13(2H, d), 1.98-1.95(2H, m)

**Example 27**

***Cis-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(2-methyl-5-(1-piperazinylmethyl)phenyl)acetamide, hydrochloride salt***



5 **i) 1,1-Dimethylethyl, 4-((4-methyl-3-nitrophenyl)methyl)piperazine-1-carboxylate**

A mixture of 4-methyl-3-nitrobenzyl chloride (5.55g), 1,1-dimethylethyl, piperazine-1-carboxylate (5.6g), N,N-diisopropylethylamine (5ml) in N,N-dimethylformamide (25ml) were heated at 110 °C for 3h. After cooling to ambient temperature the mixture was partitioned between dichloromethane and water. The organic phase collected, dried  
 10 (MgSO<sub>4</sub>) and solvent evaporated under reduced pressure to leave the subtitle compound as a pale yellow oil. Yield: 9.6g

MS: APCI(+ve) 336 (M+1)

15 **ii) 1,1-Dimethylethyl, 4-((3-amino-4-methylphenyl)methyl)piperazine-1-carboxylate**

The product from step (i) (9.6g), 10% palladium on charcoal (100mg) in ethanol (100ml) was stirred under an atmosphere of hydrogen gas for 24h. The catalyst was filtered through celite and the mother liquor collected and solvent evaporated under reduced pressure to  
 20 give the subtitle compound as a pale yellow oil. Yield. 9g

MS: APCI(+ve) 322 (M+1)

**iii) *cis-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(2-methyl-5-((4-(1,1-dimethylethyloxycarbonyl)piperazin-1-yl)methyl)phenyl)acetamide***

The product from Example 9 step (ii) (0.21 g), the product from step (ii) (0.15 g), benzotriazol-1-yl-oxy-tripyrrolidinophosphonium hexfluorophosphate (PyBrop) (0.24 g), N,N-diisopropylethylamine (0.36 ml) in dry N,N-dimethylformamide were stirred together under nitrogen for 20 h. The mixture was poured into water and the resulting precipitate  
5 filtered as an off white solid. Purification was by silica gel chromatography eluting with ethyl acetate to give the subtitle compound as a white solid. Yield: 0.21 g

MS: APCI (+ve) 594 (M+1)

10 **iv) *Cis*-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(2-methyl-5-(1-piperazinylmethyl)phenyl)acetamide, hydrochloride salt**

The product from step (iii) (0.17 mg) was dissolved in 4M hydrogen chloride in 1,4-dioxane (2 ml). After 48 h the solvents were evaporated under reduced pressure to leave the title compound as a white solid. Yield: 0.16 g

15

MS: APCI (+ve) 494 (M+1)

<sup>1</sup>H NMR: δ (DMSO) 8.50(s, 1H), 7.78(s, 1H), 7.65(d, 1H), 7.58(d, 1H), 7.39(d, 1H), 7.31(d, 1H), 5.25(m, 1H), 5.05(bs, 2H), 4.23(s, 2H), 3.77(bs, 2H), 3.43(s, 4H), 3.18(m, 6H), 3.04(m, 2H), 2.71(s, 1H), 2.30(s, 3H), 1.47(d, 6H)

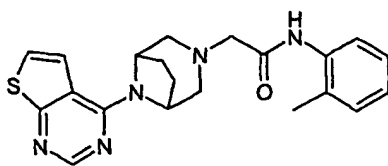
20

#### **Example 28**

***N*-(2-Methylphenyl)-2-[(8-(thieno[2,3-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl)acetamide**

25

52



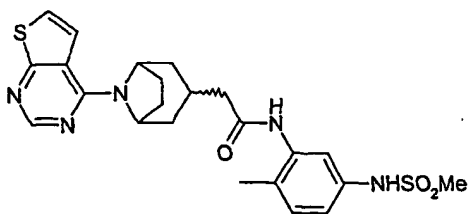
The title compound was prepared from the product of Example 20 step (iv) (0.45g) and 4-chloro-thieno[2,3-*d*]pyrimidine by the method of Example 1 step (i). Yield: 0.22g.

5 MS: APCI(+ve) 394 (M+1)

<sup>1</sup>H NMR:  $\delta$  (DMSO) 9.17 (1H, brs), 8.39 (1H, s), 7.73-7.62 (3H,m), 7.25-7.15 (2H,m), 7.07 (1H,m), 5.05 (2H,brs), 3.12 (2H,s), 2.92 (2H,d), 2.58 (2H,d), 2.28 (3H,s), 2.15 (2H,m), 1.97 (2H,m).

#### 10 Example 29

**N-[5-(Methanesulfonylamido-2-methylphenyl)-2-[8-(thieno[2,3-*d*]pyrimidin-4-yl)-8-azabicyclo[3.2.1]oct-3-yl]acetamide**



15

#### i) Ethyl, 2-(8-(thieno[2,3-*d*]pyrimidin-4-yl)-8-azabicyclo[3.2.1]oct-3-yl)ethanoate

Ethyl, 2-(8-azabicyclo[3.2.1]oct-3-yl)ethanoate (0.64g) (Arch. Pharm., 1976, 309(6), 447.

Arch. Pharm., 1975, 308(5), 365), 4-chlorothieno[2,3-*d*]pyrimidine (0.55g), N,N-diisopropylethylamine (1.7ml) in 1,4-dioxane (10ml) were heated at 105 °C for 4h. The

20 precipitate was filtered and the mother liquor collected, the solvent evaporated under reduced pressure to leave a brown oil. Purification was by silica gel chromatography eluting with ethyl acetate/iso-hexane (3:7) to give the subtitle compound as a colourless oil. Yield: 0.35g.

MS: APCI(+ve) 332 (M+1)

**ii) 2-(8-(Thieno[2,3-*d*]pyrimidin-4-yl)-8-azabicyclo[3.2.1]oct-3-yl)ethanoic acid**

The product from step (i) (0.14g) in ethanol (0.3ml) was treated with 1N sodium hydroxide (0.6ml) at ambient temperature for 48h. The mixture was acidified to pH4 with 2N hydrochloric acid and the solvents evaporated under reduced pressure. The residue was treated with ethanol (5ml) and inorganic salts filtered. The mother liquor collected and solvent evaporated under reduced pressure to leave a gummy residue. Purification was by trituration with diethyl ether. Yield: 0.097g

MS: APCI(+ve) 304 (M+1)

**iii) N-[5-bis((Methanesulphonyl)amido-2-methylphenyl)-2-[8-(thieno[2,3-*d*]pyrimidin-4-yl)-8-azabicyclo[3.2.1]oct-3-yl]acetamide**

The product from step (ii) (0.097g), the product from Example 11 step (ii) (0.089g), benzotriazol-1-yl-oxy-tripyrrolidinophosphonium hexfluorophosphate (PyBrop) (0.16g), 4-N,N-dimethylaminopyridine (0.04g), N,N-diisopropylethylamine (0.28ml) in dichloromethane (10ml) were stirred at ambient temperature for 48h. The mixture was partitioned between water and dichloromethane. The organic phase collected, dried (MgSO<sub>4</sub>) and solvent evaporated under reduced pressure. Purification was by reverse phase HPLC eluting with 1% aq. ammonium acetate/acetonitrile (90% to 50%) to give the subtitle compound as a white solid. Yield: 0.1g

MS: APCI (+ve) 564 (M+1)

**iv) N-[5-(Methanesulphonylamido-2-methylphenyl)-2-[8-(thieno[2,3-*d*]pyrimidin-4-yl)-8-azabicyclo[3.2.1]oct-3-yl]acetamide**

The product from step (iii) (0.1g), potassium carbonate (0.14g), water (5ml) and 1,4-dioxane (5ml) were heated at 110 °C for 1h. The mixture was treated with acetic acid (2ml) and solvents evaporated under reduced pressure. Purification was by silica gel

chromatography eluting with ethyl acetate to give the title compound as a white solid.

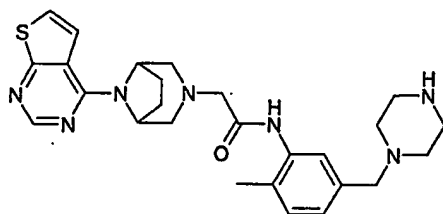
Yield: 0.011g

MS: APCI (+ve) 486 (M+1)

<sup>1</sup>H NMR:  $\delta$  (DMSO) 9.33(bs, 1H), 9.16(bs, 1H), 8.38(2xs, 1H), 7.6(m, 3H), 7.30(m, 1H), 7.15(t, 1H), 6.90(m, 1H), 5.0(bm, 2H), 2.90(s, 3H), 2.30-1.89(bm, 4H), 2.10(s, 3H), 1.5-0.9(bm, 2H)

### Example 30

*N*-(2-Methyl-5-(1-piperazinylmethyl)phenyl)-2-[(8-(thieno[2,3-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide



i) Methyl, 2-(8-(1,1-dimethylethoxyloxycarbonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl)acetate

A mixture of 1,1-dimethylethyl, 3,8-diazabicyclo[3.2.1]oct-8-carboxylate (0.35g), sodium bicarbonate (84mg), potassium iodide (20mg) and methyl bromoacetate (355mg) in ethanol (5ml) were heated at 70 °C for 6h. The reaction mixture was partitioned between ethyl acetate and water. The organic phase collected, dried (MgSO<sub>4</sub>) and the solvent evaporated under reduced pressure to leave the subtitle compound as a pale yellow solid.

Yield: 380mg

<sup>1</sup>H NMR:  $\delta$  (DMSO) 4.01 (bs, 2H), 3.58 (s, 2H), 3.29 (s, 3H), 2.62-2.49 (m, 4H), 1.82-1.64(m, 4H), 1.40 (s, 9H)

ii) Methyl, 2-(3,8-diazabicyclo[3.2.1]oct-3-yl)acetate, trifluoroacetic acid salt

The subtitle compound was prepared from the product of step (i) (380mg) by the method of Example 1 step (ii). The product was used without further purification directly in next step.

**iii) Methyl, 2-(8-(thieno[2,3-*d*]pyrimidin-4-yl)-(3,8-diazabicyclo[3.2.1]oct-3-yl)acetate**

The subtitle compound was prepared from the product of step (ii) (400mg) and 4-chloro-thieno[2,3-*d*]pyrimidine (288mg), N,N-diisopropylethylamine (232ul) in 1,4-dioxane at  
100 °C for 48h. Solvent was evaporated under reduced pressure. Purification was by silica  
gel chromatography eluting with 2% ethanol in dichloromethane to give the subtitle  
compound as a beige solid. Yield: 170mg.

MS: APCI (+ve) 319 (M+1, 100%)

**iv) 2-(8-(Thieno[2,3-*d*]pyrimidin-4-yl)-(3,8-diazabicyclo[3.2.1]oct-3-yl)acetic acid**

The product from step (iii) (170mg) was dissolved in ethanol (1ml) and treated with 1N sodium hydroxide solution (0.8ml) at room ambient temperature. After 3h the mixture was acidified with 2M hydrochloric acid to pH4. The solvents were then evaporated under  
reduced pressure and the residue treated with ethanol and filtered to remove inorganic salts.  
The mother liquor was collected and evaporated under reduced pressure to leave the  
subtitle compound as a white solid. Yield: 160mg.

MS: APCI(+ve) 305 (M+1)

**v) N-(5-(4-(1,1-Dimethylethoxy)carbonyl)piperazin-1-ylmethyl)-2-methylphenyl)-2-[(8-(thieno[2,3-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide**

The product of step (iv) (83mg), the product of Example 27 step (ii) (92mg), benzotriazol-1-yl-oxy-tripyrrolidinophosphonium hexafluorophosphate (PyBrop) (153mg) and N,N-diisopropylethylamine (95ul) were stirred in N,N-dimethylformamide (5ml) at ambient  
temperature for 12h. The solvents were evaporated under reduced pressure and purification  
was by silica gel chromatography eluting with iso-hexane/acetone (7:3) containing 1%  
triethylamine to give the subtitle compound as a white solid. Yield: 40mg.



<sup>1</sup>H NMR δ (DMSO) 9.15(s, 1H), 8.38(s, 1H), 7.67-7.66(m, 2H), 7.17(d, 1H), 7.00(d, 1H), 5.04(bs, 2H), 3.41(s, 2H), 3.29(s, 4H), 3.11(s, 2H), 2.90(d, 2H), 2.29(t, 4H), 2.24(s, 3H), 2.14(d, 2H), 2.00-1.93(m, 2H), 1.38(s, 9H)

- 5 vi) *N*-(2-Methyl-5-(1-piperazinylmethyl)phenyl)-2-[(8-(thieno[2,3-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide

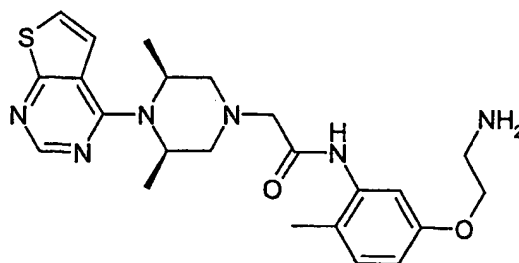
The title compound was prepared from the product of step (v) (35mg) by the method of Example 8 step (iv) as a white solid. Yield: 35mg

- 10 MS: APCI(+ve) 492 (M+1)

<sup>1</sup>H NMR: δ (DMSO) 9.66(bs, 1H), 8.53(s, 1H), 7.75 (s, 2H), 7.63(bs, 1H), 7.42(d, 1H), 7.33(d, 1H), 5.21(bs, 2H), 4.33 (bs, 2H), 3.79-3.13(bm, 10H), 2.40-2.26(bm, 4H), 2.23(s, 3H), 2.20-2.10(bm, 4H).

15 **Example 31**

*Cis-N*-(5-(2-Aminoethoxy)-2-methyl-phenyl)-2-(3,5-dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)acetamide, hydrochloride salt



- i) 1,1-Dimethylethyl, 2-(4-methyl-3-nitro-phenoxy)ethylamino-1-carboxylate

- 20 The subtitle compound was prepared from 4-methyl-3-nitrophenol (2g) and 1,1-dimethylethyl, 2-hydroxyethylamino-1-carboxylate (2.5g) by the method of Example 50 step (i) as a beige solid. Yield: 3g

- <sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 7.50(s, 1H), 7.22(d, 1H), 7.05(dd, 1H), 4.96(bs, 1H), 4.07(t, 2H),  
25 3.56(q, 2H), 2.52(s, 3H), 1.46(s, 9H)

**ii) 1,1-Dimethylethyl, 2-(3-amino-4-methyl-phenoxy)ethylamino-1-carboxylate**

The subtitle compound was prepared from the product of step (i) (1g) by the method of Example 50 step (ii) as an off white solid. Yield: 0.9g

5 MS: APCI (+ve) 267 (M+1)

**iii) cis-N-(5-(2-(1,1-Dimethylethyloxycarbonylaminoethoxy))-2-methyl-phenyl)-2-(3,5-dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)acetamide**

The product of Example 9 step (ii) (0.54g), the product from step (ii) (0.35g), benzotriazol-  
10 1-yl-oxy-tripyrrolidinophosphonium hexafluorophosphate (PyBrop) (0.59g), N,N-diisopropylethylamine (0.8ml) in dry N,N-dimethylformamide (15ml) were stirred together under nitrogen for 24h. The mixture was poured onto water (50ml) and the resulting precipitate filtered as a pale yellow solid. Purification was by silica gel chromatography eluting with diethyl ether/ethyl acetate (9:1) as eluant to give the subtitle compound as a  
15 white solid. Yield: 0.51g

MS: APCI(+ve) 555 (M+1)

**iv) Cis-N-(5-(2-Aminoethoxy)-2-methyl-phenyl)-2-(3,5-dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)acetamide, hydrochloride salt**  
20

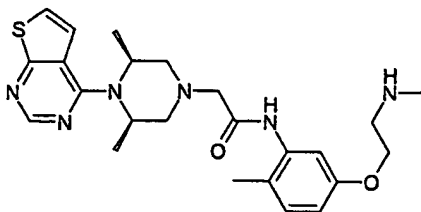
The title compound was prepared from the product of step (iii) (0.42g) according to the method of Example 27 step (iv) as a white solid. Yield: 0.36g

MS: APCI(+ve) 455 (M+1)

25 <sup>1</sup>HNMR  $\delta$  (DMSO) 9.57(bs, 1H), 8.50(s, 1H), 8.15(bs, 2H), 7.65(d, 1H), 7.57(d, 1H), 7.37(s, 1H), 7.15(d, 1H), 6.75(dd, 1H), 5.05(bs, 2H), 4.17(t, 2H), 3.77(bs, 2H), 3.27(d, 2H), 3.19(d, 2H), 3.00(bs, 2H), 2.22(s, 3H), 1.48(d, 6H)

**Example 32**

***Cis-N-(5-(2-(N-Methylamino)ethoxy)-2-methyl-phenyl)-2-(3,5-dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)acetamide, hydrochloride salt***



- 5    **i) 1,1-Dimethylethyl, 2-(4-methyl-3-nitro-phenoxy)ethyl(N-methylamino)-1-carboxylate**

The subtitle compound was prepared from 4-methyl-3-nitrophenol (0.5g) and 1,1-dimethylethyl, 2-hydroxyethyl-(N-methylamino)-1-carboxylate (0.69g) by the method of Example 50 step (i) as a beige solid. Yield: 0.67g

10

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 7.5(s, 1H), 7.24(d, 1H), 7.61(dd, 1H), 4.12(bs, 2H), 3.64(t, 2H), 2.98(s, 3H), 2.53(s, 3H), 1.46(s, 9H)

- 15    **ii) 1,1-Dimethylethyl, 2-(3-amino-4-methyl-phenoxy)ethyl(N-methylamino)-1-carboxylate**

The subtitle compound was prepared from the product of step (i) (1g) by the method of Example 50 step (ii) as an off white solid. Yield: 0.95g

MS: APCI (+ve) 281 (M+1)

20

- iii) *N*-(5-(2-(1,1-Dimethylethoxycarbonyl(N-methylamino)ethoxy))-2-methyl-phenyl)-2-(3,5-dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)acetamide**

The subtitle compound was prepared from the product of Example 9 step (ii) (0.26g), the product of step (ii) (0.175g) by the method of Example 31 step (iii). Purification was by  
25    silica gel chromatography eluting with diethyl ether/ethyl acetate (9:1) as eluant to give the subtitle compound as a white solid. Yield: 0.25g

MS: APCI(+ve) 569 (M+1)

iv) *cis-N*-(5-(2-(N-Methylamino)ethoxy)-2-methyl-phenyl)-2-(3,5-dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)acetamide, hydrochloride salt

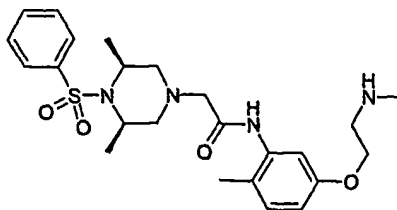
- 5 The title compound was prepared from the product of step (iii) (0.189g) by the method of Example 27 step (iv) as a white solid. Yield: 0.077g

MS: APCI(+ve) 469 (M+1)

- <sup>1</sup>HNMR  $\delta$  (DMSO ) 9.50(bs, 1H), 9.00(bs, 1H), 8.49(s, 1H), 7.64(d, 1H), 7.57(d, 1H),  
10 7.39(s, 1H), 7.17(d, 1H), 6.76(d, 1H), 5.05(bs, 2H), 4.24(s, 2H), 3.22-3.30(m, 4H), 2.95(bs, 2H), 2.62(s, 2H), 2.22(s, 3H), 1.48(d, 6H)

### Example 33

- Cis-N*-(5-(2-(N-Methylamino)ethoxy)-2-methyl-phenyl)-2-(4-benzenesulphonyl)-3,5-dimethyl)piperazin-1-yl)acetamide  
15



i) *cis*-1,1-Dimethylethyl, (4-benzenesulphonyl-3,5-dimethyl)piperazine-1-carboxylate

- A solution of *cis*-1,1-dimethyl, 3,5-dimethylpiperazine-1-carboxylate (5g) in pyridine  
20 (60ml) was treated with benzene sulphonyl chloride (3ml). After 48h the solvent was evaporated under reduced pressure and purification of the residue was by silica gel chromatography eluting with ethyl acetate containing 1% triethylamine to give the subtitle compound as a yellow solid. Yield: 5g

- 25 MS: APCI(+ve) 255 (M-99)

ii) *cis*-1-Benzenesulphonyl-3,5-dimethylpiperazine, trifluoroacetic acid salt

The subtitle compound was prepared from the product of step (i) (5g) by the method Example 1 step (ii). Purification was by recrystallisation from ethanol. Yield: 2g

MS: APCI(+ve) 255 (M+1)

5

**iii) *Cis-2-chloro-N-[5-(2-(1,1-dimethylethoxycarbonyl)-N-methylamino)ethoxy]-2-methyl-phenyl]acetamide***

A solution of the product from Example 32 step (ii) (0.65g), N,N-diisopropylethylamine (1ml) in dichloromethane (30ml) at 0 °C under nitrogen was treated with chloroacetyl chloride (202ul). After 2h the mixture was partitioned with water and the product extracted into dichloromethane. The organic phase collected, dried (MgSO<sub>4</sub>) and solvent removed under reduced pressure to give the subtitle compound as a beige foam. Yield: 0.9g

MS: APCI (-ve) 355 (M-1)

15

**iv) *Cis-N-(5-(2-((1,1-dimethylethoxycarbonyl)-N-methylamino)ethoxy)-2-methyl-phenyl)-2-(4-benzenesulphonyl)-3,5-dimethyl)piperazin-1-yl)acetamide***

The product of step (ii) (100mg), sodium bicarbonate (99mg), potassium iodide (5mg) in ethanol (6ml) was treated with the product of step (iii) at 70 °C for 12h. The mixture was partitioned between ethyl acetate and water. The organic phase collected, dried (MgSO<sub>4</sub>) and solvent evaporated under reduced pressure. Purification was by silica gel chromatography eluting with iso-hexane/acetone (7:3) containing 1% triethylamine to give the subtitle compound as a white solid. Yield: 126mg

MS: APCI(+ve) 575 (M+1), APCI(-ve) 573 (M-1)

25

**v) *Cis-N-(5-(2-(N-Methylamino)ethoxy)-2-methyl-phenyl)-2-(4-benzenesulphonyl)-3,5-dimethyl)piperazin-1-yl)acetamide, hydrochloride salt***

The title compound was prepared from the product of step (iv) (120mg) by the method of Example 27 step (ii) as a white solid. Yield: 107mg

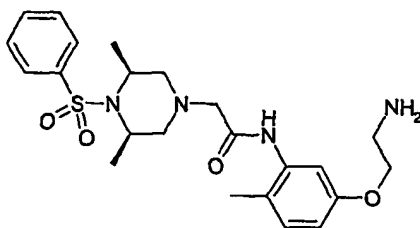
30

MS: APCI(+ve) 475 (M+1), APCI (-ve) 473 (M-1)

<sup>1</sup>H NMR  $\delta$  (DMSO) 9.01(bs, 2H), 7.85(d, 2H), 7.69(t, 1H), 7.62(t, 2H), 7.30(bs, 1H),  
7.15(d, 1H), 6.74(dd, 1H), 4.18(t, 4H), 4.01(bs, 2H), 3.56(s, 2H), 3.31-3.25(m, 2H), 2.61-  
2.58(m, 3H), 2.50 (m, 2H), 2.15(s, 3H), 1.44 (d, 6H)

### Example 34

***Cis-N-[5-(2-Aminoethoxy)-2-methyl-phenyl]-2-(4-benzenesulphonyl-3,5-dimethyl)piperazin-1-yl]acetamide, hydrochloride salt***



i) ***Cis-2-chloro-N-[5-(2-(1,1-dimethylethoxycarbonyl)amino)ethoxy-2-methyl-phenyl]acetamide***

The subtitle compound is prepared from the product of Example 31 step (ii) (650mg) and chloroacetyl chloride (213ul) by the method of Example 33 step (iii) as a beige foam.

Yield: 900mg

MS: APCI(-ve) 341 (M-1)

ii) ***Cis-N-[5-(2-(1,1-Dimethylethoxycarbonyl)amino)ethoxy-2-methyl-phenyl]-2-(4-benzenesulphonyl-3,5-dimethyl)piperazin-1-yl]acetamide***

The subtitle compound was prepared from the product of step (i) (148mg) and the product of Example 33 step (ii) by the method of Example 33 step (iv) as a pale yellow solid. Yield: 150mg.

MS: APCI(+ve) 561 (M+1), APCI (-ve) 559 (M-1)

**iii) *Cis-N*-[5-(2-(Aminoethoxy)-2-methyl-phenyl)-2-(4-benzenesulphonyl-3,5-dimethyl)piperazin-1-yl]acetamide, hydrochloride salt**

The title compound was prepared from the product of step (ii) (150mg) by the method Example 27 step (iv) as a white solid. Yield: 150mg

5

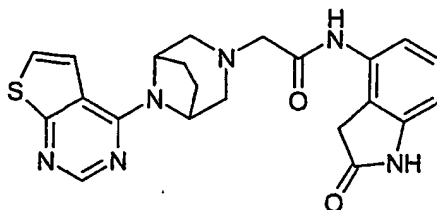
MS: APCI (+ve) 461(M+1), APCI (-ve) 459 (M-1)

<sup>1</sup>H NMR  $\delta$  (DMSO) 8.13(bs, 2H), 7.85(d, 2H), 7.70-7.59(m, 3H), 7.32(bs, 1H), 7.14(d, 1H), 6.73(dd, 1H), 4.16(bs, 2H), 4.10(t, 2H), 3.56(s, 2H), 3.19(d, 2H), 3.10-3.03(m, 2H), 2.50(m, 2H), 2.15(s, 3H), 1.43 (d, 6H)

10

**Example 35**

***N*-(2-Oxo-2,3-dihydro-1*H*-indol-4-yl)-2-(8-thieno[2,3-*d*]pyrimidin-4-yl-3,8-diazabicyclo[3.2.1]oct-3-yl)acetamide**



**i) 2-Chloro-*N*-(2-oxo-2,3-dihydro-1*H*-indol-4-yl)acetamide**

The subtitle compound was prepared from 4-amino-oxindole (0.19g) (J. Org. Chem., 1983, 48 (15), 2468-72) and chloroacetyl chloride (0.1ml) by the method of Example 15 step (i). Yield: 0.25g

20 MS: ES(-ve) 223 (M-1)

**ii) 3-[(2-Oxo-2,3-dihydro-1*H*-indol-4-yl)carbamoyl]-methyl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylic acid, 1,1-dimethylethyl ester**

The subtitle compound was prepared from the product of step (i) (0.24g) and 1,1-dimethyl,

25 3,8-diaza-bicyclo[3.2.1]octane-8-carboxylate (0.26g) by the method of Example 19 step (i)

Yield: 0.8g

<sup>1</sup>H NMR: δ (DMSO) 10.45 (1H,s), 9.26 (1H,s), 7.39 (1H,d), 7.15 (1H,t), 6.62 (1H,d), 4.06 (2H,brs), 3.45 (2H,s), 3.10 (2H,s), 2.72 (2H,d), 2.38 (2H,d), 1.95 (2H,d), 1.79 (2H,m), 1.41 (9H,s).

iii) 2-(3,8-Diazabicyclo[3.2.1]oct-3-yl)-N-(2-oxo-2,3-dihydro-1H-indol-4-yl)acetamide, hydrochloride salt

The product of step (ii) (0.8g) was dissolved in 2M hydrogen chloride in 1,4-dioxane (10ml), 1,4-dioxane (10ml), methanol (10ml) and the reaction mixture was stirred at ambient temperature for 2 hours. The solvents evaporated under reduced pressure to dryness. Yield: 0.8g

MS: ES(+ve) 301 (M+1)

iv) N-(2-Oxo-2,3-dihydro-1H-indol-4-yl)-2-(8-thieno[2,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl)acetamide

The title compound was prepared from the product of step (iii) (0.8g) by the method of Example 1 step (i). Yield: 0.1g

MS: ES(+ve) 435 (M+1)

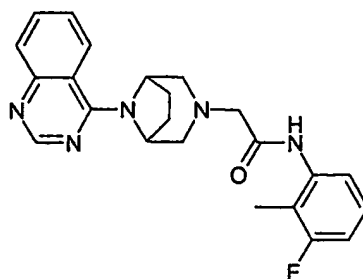
<sup>1</sup>H NMR: δ (DMSO) 10.43 (1H,s), 9.27 (1H,s), 8.39 (1H,s), 7.66 (1H,d), 7.62 (1H,d), 7.40 (1H,d), 7.15 (1H,t), 6.62 (1H,d), 5.04 (2H,brs), 3.47 (2H,s), 3.12 (2H,s), 2.87 (2H,d), 2.57 (2H,d), 2.15 (2H,m), 1.97 (2H,m).

M.P. 265°C decomp.

### Example 36

N-(3-Fluoro-2-methyl-phenyl)-2-((8-quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl)acetamide





**i) 2-Chloro-N-(3-fluoro-2-methyl-phenyl)acetamide**

The subtitle compound was prepared from 3-fluoro-2-methylaniline (0.232g) and chloroacetyl chloride (0.164ml) by the method of Example 33 step (iii) as a beige solid.

5 Yield: 0.3g

MS: APCI(-ve) 200 (M-1)

**ii) N-(3-Fluoro-2-methyl-phenyl)-2-(1,1-dimethylethyloxycarbonyl)-3,8-**

10 **diazabicyclo[3.2.1]oct-3-yl]acetamide**

The subtitle compound was prepared from the product of step (i) (179mg) and 1,1-dimethyl-3,8-diaza-bicyclo[3.2.1]octane-8-carboxylate (0.2g) by the method of Example 33 step (iv) as a white solid. Yield: 305mg

15 MS: APCI (+ve) 378 (M+1)

**iii) N-(3-Fluoro-2-methyl-phenyl)-2-(3,8-diazabicyclo[3.2.1]oct-3-yl)acetamide, hydrochloride salt**

20 The subtitle compound was prepared from the product of step (ii) (303mg) by the method of Example 27 step (iv) as a white solid. Yield: 305mg

MS: APCI(+ve) 278 (M+1), APCI (-ve) 276 (M-1)

**iv) N-(3-Fluoro-2-methyl-phenyl)-2-((8-quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl)acetamide**

25

The title compound was prepared from the product of step (iii) (223mg) and 4-chloroquinazoline (133mg) by the method of Example 2 step (i) as a white solid.

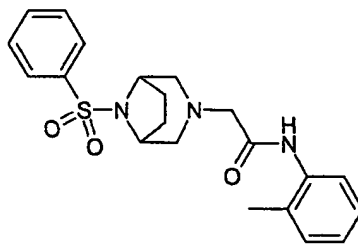
Yield: 120mg

5 MS: APCI(+ve) 406 (M+1)

<sup>1</sup>H NMR  $\delta$  (DMSO) 9.34 (s, 1H), 8.57(s, 1H), 8.09(d, 1H), 7.84-7.77(m, 2H), 7.60-7.53(m, 2H), 7.22(q, 1H), 6.99(t, 1H), 4.87(bs, 2H), 3.24(s, 2H), 2.97(dd, 2H), 2.77(dd, 2H), 2.17(s, 3H), 2.12-2.04(m, 2H), 1.91-1.85(m, 2H)

10 **Example 37**

*N*-(2-Methylphenyl)-2-[8-(benzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide



The trifluoroacetate salt of Example 20 step (iv) was converted to the free base by use of aqueous 2N NaOH solution followed by extraction with ethyl acetate. The extracts were dried (MgSO<sub>4</sub>), filtered and evaporated to dryness, leaving an oil which crystallised on standing.

MS: ES(+ve) 260 (M+1, 100%)

20

The amine free base (0.075g) was stirred in acetone (15ml) and a solution of K<sub>2</sub>CO<sub>3</sub> (0.08g) in water (0.5ml) was added, followed by benzenesulphonyl chloride (0.047g) dissolved in acetone (5.0ml). The solution was stirred for 1 hour, quenched with water and the white solid was collected by filtration, washed with water and dried *in vacuo*, to give the title compound. Yield 0.037g.

25

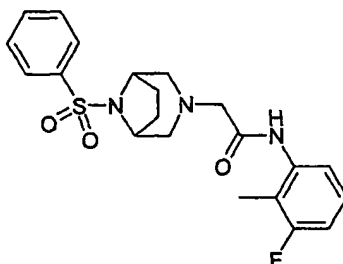
MS: APCI(+ve) 487 (M+1, 100%)

$^1\text{H}$  NMR:  $\delta$  ( $\text{CDCl}_3$ ) 1.55 (s,  $\text{H}_2\text{O}$ ), 1.70 (2H, m), 1.85 (2H, m), 2.26 (3H, s), 2.67 (2H, m), 2.85 (2H, d of d), 3.18 (2H, s), 7.05 (2H, m), 7.2 (2H, m), 7.52 (2H, m), 7.6 (1H, m), 7.9 (2H, d)

5 MP: 169-170 °C

### Example 38

*N*-(3-Fluoro-2-methylphenyl)-2-[8-(benzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide



10

#### i) Methyl, (3,8-Diazabicyclo[3.2.1]oct-3-yl)acetate, hydrochloride salt

A mixture of the product from Example 30 step (i), 2M HCl in 1,4-dioxane (10ml) and methanol (10ml) was stirred at ambient temperature for 2 hours and evaporated to dryness. Yield 0.54g. Used directly in the next step.

15

#### ii) Methyl, (8-benzenesulphonyl-3,8-diazabicyclo[3.2.1]oct-3-yl)acetate

A mixture of the product of step (i) (0.53g), potassium carbonate (0.66g) and benzenesulphonyl chloride (0.32ml) in acetone (10ml) and 1,4-dioxane (10ml) was stirred at ambient temperature for 4 hours. The mixture was partitioned between ethyl acetate and water. The organic phase was washed with water, saturated sodium bicarbonate and brine, dried ( $\text{MgSO}_4$ ) and evaporated. The product was purified by silica gel chromatography eluting with 0.5% ethanol in dichloromethane. Yield 0.29g.

20

$^1\text{H}$  NMR:  $\delta$  (DMSO) 7.86 (2H,d), 7.69 (1H,m), 7.59 (2H,m), 4.13 (2H,brs), 3.59 (3H,s), 3.29 (2H,s), 2.67 (2H,dd), 2.57 (2H,d), 1.59 (2H,q), 1.13 (2H,m).

25

**iii) (8-Benzenesulphonyl-3,8-diazabicyclo[3.2.1]oct-3-yl)acetic acid**

A solution of the product of step (ii) (0.29g) in ethanol (5ml) was treated with 1ml of 1N sodium hydroxide solution. After 1 hour at ambient temperature the reaction mixture was acidified with 2N hydrochloric acid to pH4 and evaporated to dryness to give a white solid.

- 5 This was dried at 40°C *in vacuo* over phosphorous pentoxide for 2 hours and used directly in the next step.

**iv) *N*-(3-Fluoro-2-methylphenyl)-2-[8-(benzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide**

- 10 A mixture of the product of step (iii) (0.45mmol), 2-fluoro-2-methylaniline (60µl), PyBroP (0.25g), *N,N*-dimethylaminopyridine (54mg) and *N,N*-diisopropylethylamine (0.23ml) in *N,N*-dimethylformamide (5ml) was stirred at ambient temperature for 16 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with water and brine, dried (MgSO<sub>4</sub>) and evaporated. The residue was purified by  
15 flash chromatography eluting with 1% ethanol in dichloromethane followed by further chromatography with 20% ethyl acetate /iso-hexane to give the title compound as a white solid. Yield: 30mg.

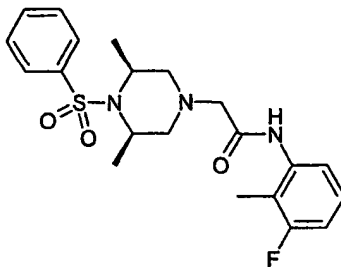
MS: AP (+ve) 418 (M+1)

- 20 <sup>1</sup>H NMR: δ (DMSO) 9.20 (1H,s), 7.88 (2H,d), 7.70 (1H,m), 7.60 (2H,m), 7.49 (1H,d), 7.20 (1H,q), 6.97 (1H,t), 4.17 (2H,brs), 3.17 (2H,s), 2.81 (2H,dd), 2.50 (2H,d), 2.09 (3H,s), 1.78 (2H,m), 1.20 (2H,m).

M.P. 168-9°C

**25 Example 39**

***Cis-N*-(3-Fluoro-2-methyl-phenyl)-2-(4-benzenesulphonyl)-3,5-dimethyl)piperazin-1-yl)acetamide**



**i) *Cis-N-(3-Fluoro-2-methyl)phenyl)-2-(4-benzenesulphonyl)-3,5-dimethylpiperazin-1-yl)acetamide***

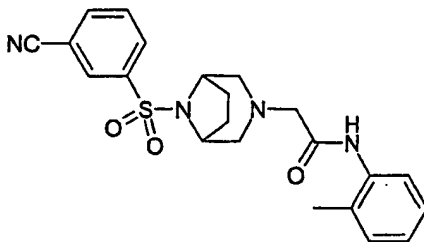
The title compound was prepared from the product of Example 33 step (ii) (152mg) and  
 5 the product of Example 36 step (i) (132mg) by the method of Example 33 step (iv) as a  
 white solid. Purification was by silica gel chromatography eluting with iso-hexane/acetone  
 (7:3). Yield: 58mg.

MS: APCI(+ve) 420 (M+1)

10 <sup>1</sup>H NMR δ (DMSO) 9.23(s, 1H), 7.83(d, 2H), 7.69-7.58(m, 3H), 7.34(d, 1H), 7.20(q, 1H),  
 6.99(t, 1H), 4.06-3.99(m, 2H), 3.03(s, 2H), 2.64(d, 2H), 2.08(s, 3H), 1.90(dd, 2H), 1.42(d,  
 6H)

**Example 40**

15 **N-(2-Methylphenyl)-2-[8-(3-cyanobenzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide**



The title compound was prepared from the product of Example 20 step (iv) and 3-  
 cyanobenzenesulphonyl chloride by the method of Example 37 as a white solid. Yield  
 20 0.101g.

MS: APCI(+ve) 425 (M+1, 100%)

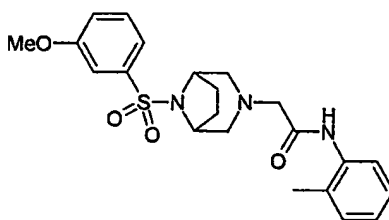
<sup>1</sup>H NMR: δ (CDCl<sub>3</sub>) 1.76(2H, m), 1.92(2H, m), 2.27(3H, s), 2.64(2H, d), 2.85(2H, m), 3.20(2H, s), 4.26(2H, s), 7.06(1H, m), 7.20(2H, m), 7.68(1H, m), 7.87(1H, m), 8.02(1H, d), 8.13(1H, m), 8.18(1H, s), 8.68(1H, s)

MP: 166-8 °C

5

#### Example 41

**2-[8-(3-Methoxybenzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide**



10

The title compound was prepared from the product of Example 20 step (iv) and 3-methoxybenzenesulphonyl chloride by the method of Example 37 as a white solid  
Yield 0.095g.

15 MS: APCI(+ve) 430 (M+1, 100%)

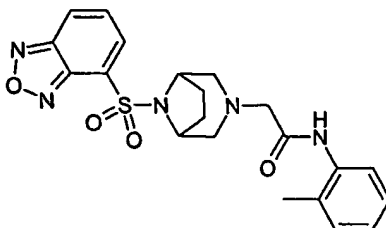
<sup>1</sup>H NMR: δ (CDCl<sub>3</sub>) 1.75(2H, m), 1.82(2H, m), 2.26(3H, s), 2.65(2H, d), 2.82(2H, d of d), 3.18(2H, s), 3.86(3H, s), 4.25(2H, br s), 7.02-7.25(4H, m), 7.40-7.50(3H, m), 8.02(1H, d), 8.75(1H, br s)

MP: 163-5 °C

20

#### Example 42

**2-[8-(Benzo[1,2,5]oxadiazole-4-sulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide**



The title compound was prepared from the product of Example 20 step (iv) by the method of Example 37 as a white solid. Yield: 0.088g.

5 MS: APCI(+ve) 442 (M+1, 100%)

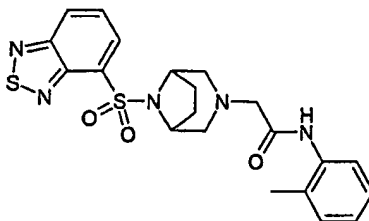
<sup>1</sup>H NMR: δ (CDCl<sub>3</sub>) 1.90-2.02(4H, m), 2.28(3H, s), 2.65(2H, m), 2.90(2H, m),  
3.16(2H, s), 4.55(2H, s), 7.06(1H, m), 7.19(2H, m), 7.54(1H, m), 8.08(3H, d),  
8.75(1H, br s)

MP: 167-8 °C

10

### Example 43

**2-[8-(Benzo[1,2,5]thiadiazole-4-sulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide**



15 The title compound was prepared from the product of Example 20 step (iv) by the method of Example 37 as a white solid. Yield 0.108g.

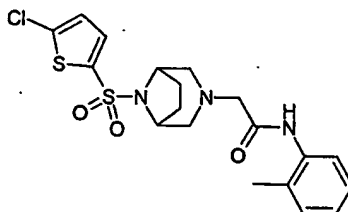
MS: APCI(+ve) 458 (M+1, 100%)

<sup>1</sup>H NMR: δ (CDCl<sub>3</sub>) 1.75(2H, m), 1.93(2H, m), 2.27(3H, s), 2.62(2H, m), 2.85(2H, d of d),  
20 3.14(2H, s), 4.61(2H, br s), 7.05(1H, m), 7.20(2H, m), 7.70(1H, m), 8.02(1H, d),  
8.26(2H, d of d), 8.77(1H, br s)

MP: 169-70 °C

**Example 44**

**2-[8-(5-Chlorothieno-2-yl)sulphonyl]-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide**



5

The title compound was prepared from the product of Example 20 step (iv) and 2-chloro-5-chlorosulphonyl-thiophene by the method of Example 37 as a white solid. Yield 0.108g.

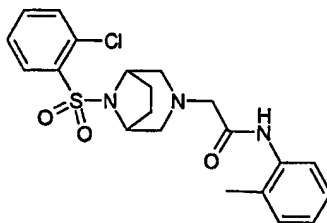
MS: APCI(+ve) 440 (M+1, 100%)

10 <sup>1</sup>H NMR:  $\delta$  (CDCl<sub>3</sub>) 1.90(4H, m), 2.28(3H, s), 2.70(2H, d), 2.86(2H, m), 3.21(2H, s), 4.27(2H, br s), 6.94(1H, d), 7.05(1H, m), 7.20(2H, m), 7.42(1H, d), 8.04(1H, d), 8.73(1H, br s)

MP: 150-2 °C

15 **Example 45**

**2-[8-(2-Chlorobenzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide**



20 The title compound was prepared from the product of Example 20 step (iv) and 2-chlorobenzenesulphonyl chloride by the method of Example 37 as a white solid. Yield 0.085g.

MS: APCI(+ve) 434 (M+1, 100%)



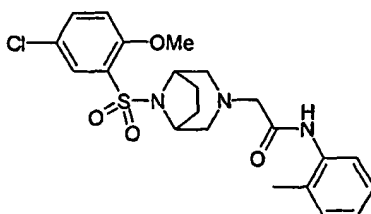
$^1\text{H}$  NMR:  $\delta$  ( $\text{CDCl}_3$ ) 2.07(4H, m), 2.31(3H, s), 2.66(2H, d), 2.82(2H, m), 3.18(2H, s), 4.31(2H, br s), 7.05(1H, m), 7.22(2H, m), 7.40(1H, m), 7.53(2H, m), 8.05(1H, d), 8.12(1H, d of d), 8.80(1H, br s)

MP: 170-1 °C

5

#### Example 46

2-[8-(5-Chloro-2-methoxybenzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide



10 The title compound was prepared from the product of Example 20 step (iv) and 3-chloro-6-methoxybenzenesulphonyl chloride by the method of Example 37 as a white solid  
Yield 0.105g.

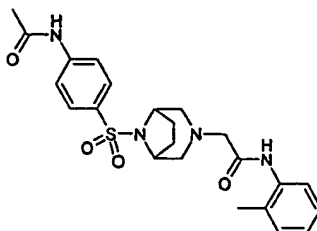
MS: APCI(+ve) 464 ( $M+1$ , 100%)

15  $^1\text{H}$  NMR:  $\delta$  ( $\text{CDCl}_3$ ) 1.93(4H, m), 2.30(3H, s), 2.62(2H, m), 2.85(2H, m), 3.17(2H, s), 3.95(3H, s), 4.35(2H, br s), 6.95(1H, d), 7.05(1H, m), 7.20(2H, m), 7.46(1H, d of d), 7.91(1H, d), 8.05(1H, d), 8.80(1H, br s)

MP: 180-1 °C

20 **Example 47**

2-[8-(4-Acetylaminomethoxybenzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide



The title compound was prepared from the product of Example 20 step (iv) and 4-acetylamidobenzenesulphonyl chloride by the method of Example 37 as a white solid.

Yield 0.108g.

5

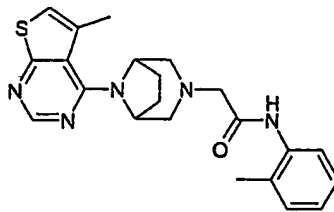
MS: APCI(+ve) 457 (M+1, 100%)

<sup>1</sup>H NMR:  $\delta$  (CDCl<sub>3</sub>) 1.60(2H, m), 1.82(2H, m), 2.18(3H, s), 2.26(3H, s), 2.65(2H, d), 2.80(2H, d of d), 3.18(2H, s), 4.20(2H, br s), 7.05(1H, m), 7.18(2H, m), 7.78(4H, s), 8.00(1H, d), 8.77(1H, br s), 9.64(1H, s)

10 MP: 205-6 °C

#### Example 48

N-(2-Methylphenyl)-2-[(8-(3-methylthieno[2,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl)acetamide



15

The trifluoroacetate salt of Example 20 step (iv) was converted to the free base by use of aqueous 2N NaOH solution followed by extraction with ethyl acetate. The extracts were dried (MgSO<sub>4</sub>), filtered and evaporated to dryness, leaving an oil which crystallised on standing.

20 MS: ES(+ve) 260 (M+1,100%)

A mixture of the amine free base (0.13g), N,N-disopropylethylamine (0.5ml), 4-dimethylaminopyrimidine (0.06g) and 4-chloro-3-methylthieno[2,3-d]pyrimidine

was heated in N-methylpyrrolidin-2-one (5.0ml) at 100 °C for 5 hours. The solvent was evaporated under high vacuum and the residue was slurried with water, filtered and dried. Purification was by chromatography on silica gel eluting with dichloromethane containing ethanol (1%) to give the title compound as a white solid. Yield (0.053g).

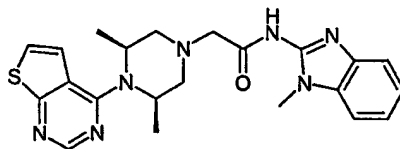
MS: APCI(+ve) 408 (M+1, 100%)

<sup>1</sup>H NMR: δ (CDCl<sub>3</sub>) 1.98(4H, m), 2.35(3H, s), 2.62(3H, s), 2.95(4H, m), 3.26(2H, s), 4.46(2H, br s), 7.00(1H, s), 7.10(1H, m), 7.20(2H, m), 8.10(1H, d), 8.53(1H, s), 8.96(1H, br s)

MP: 199-200 °C

#### Example 49

*cis*-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-*N*-(1-methyl-1*H*-benzoimidazol-2-yl)acetamide



The title compound was prepared from the product of Example 9 step (ii) (0.2g) and 2-amino-1-methyl-benzimidazole (0.14g) by the method of Example 38 step (iv). Purification was by silica gel chromatography followed by recrystallisation from methanol. Yield 45mg.

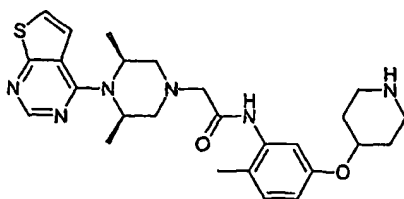
MS: APCI (+ve) 436 (M+1)

<sup>1</sup>H NMR: δ (CDCl<sub>3</sub>) 8.47 (1H,s), 7.41 (1H,d), 7.26 (3H,m), 5.01 (2H,brs), 3.68 (3H,s), 3.40 (2H,s), 3.05 (2H,d), 2.50 (2H,d), 1.61 (6H,s).

M.P. 200°C

#### Example 50

***Cis-2-(3,5-Dimethyl-4-(thieno[2,3-d]pyrimidin-4-yl)piperazin-1-yl)-N-(2-methyl-5-(4-piperidinyloxy)phenyl)acetamide, hydrochloride salt***



**i) 1,1-Dimethylethyl, 4-(4-methyl-3-nitro)phenoxy piperidine-1-carboxylate**

A solution of 4-methyl-3-nitrophenol (2g), 1,1-dimethylethyl, 4-hydroxypiperidine-1-carboxylate (2.6g), triphenylphosphine (4.11g) in tetrahydrofuran (40ml) under nitrogen at 0 °C was treated with diethylazidodicarboxylate (2.3ml) over 1 minute. The cooling bath was removed and the mixture allowed to stir at ambient temperature for 48h. The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography eluting with dichloromethane containing 1% triethylamine to give the subtitle product as a pale yellow oil. Yield: 3.46g

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 7.52(dd, 1H), 7.21(dd, 1H), 7.08(dd, 1H), 4.50(m, 1H), 3.70(m, 2H), 3.55(m, 2H), 2.50(s, 3H), 2.0-1.6(m, 4H), 1.5 (s, 9H)

**ii) 1,1-Dimethylethyl, 4-(3-amino-4-methyl)phenoxy piperidine-1-carboxylate**

A solution of the product from step (i) (2g), 10% Palladium on charcoal (300mg) were stirred under a 1 bar atmosphere of hydrogen at ambient temperature. The mixture was filtered through celite and solvent removed under reduced pressure to leave the subtitle product as a beige solid. Yield: 1.88g

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 6.9(d, 1H), 6.3(m, 2H), 4.4(m, 1H), 3.7(m, 2H), 3.6(bs, 2H), 3.3(m, 2H), 2.10(s, 3H), 1.9-1.6(m, 4H), 1.50(s, 9H)

**iii) 2-Chloro-N-5-(1-(1,1-dimethylethoxycarbonyl)-4-piperidinyloxy)-4-methyl-5-nitro)acetamide**

A solution of the product from step (ii) (1.4g), N,N-diisopropylethylamine (2ml) in dichloromethane (30ml) under nitrogen at 0 °C was treated with chloroacetylchloride (0.4ml). After 4h the reaction mixture was partitioned between water and dichloromethane. The organic phase collected, dried (MgSO<sub>4</sub>) and solvent reduced under reduced pressure to  
5 leave the subtitle compound as a brown oil. Yield: 1.8g This was used directly in the next step.

**iv) *Cis-2-(3,5-Dimethyl-4-(thieno[2,3-d]pyrimidin-4-yl)piperazin-1-yl)-N-(2-methyl-5-(1-(1,1-dimethylethoxycarbonyl)-4-piperidinyloxy)phenyl)acetamide***

10 The subtitle compound was prepared from the product of Example 2 step (ii) (0.4g) and the product of step (iii) (0.56g) by the method of Example 33 step (iv) as a pale yellow gum.  
Yield: 0.25g

MS: APCI(+ve) 595 (M+1), APCI(-ve) 593(M-1)

15

**v) *Cis-2-(3,5-Dimethyl-4-(thieno[2,3-d]pyrimidin-4-yl)piperazin-1-yl)-N-(2-methyl-5-(4-piperidinyloxy)phenyl)acetamide, hydrochloride salt***

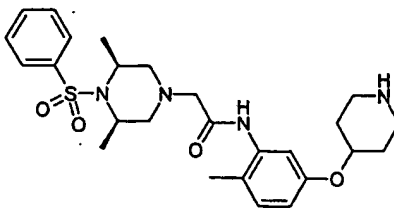
The title compound was prepared from the product of step (iv) (0.24g) by the method of Example 27 step (iv) as a white solid. Purification was by reverse phase HPLC eluting with  
20 aq. 1% ammonium acetate/acetonitrile (95% to 60%). Yield. 80mg

MS: APCI(+ve) 495(M+1), APCI(-ve) 493 (M-1)

<sup>1</sup>HNMR δ (DMSO) 8.97(bs, 1H), 8.52(s, 1H), 7.7(d, 1H), 7.62(d, 1H), 7.26(s, 1H), 7.18(d, 1H), 6.84(d, 1H), 5.30(bs, 2H), 4.60(bs, 1H), 3.30-3.00(2xbs, 4H), 2.20(s, 3H), 2.15-  
25 1.80(m, 4H), 1.60(d, 6H)

**Example 51**

***Cis-2-(3,5-Dimethyl-4-benzenesulphonyl)piperazin-1-yl)-N-(2-methyl-5-(4-piperidinyloxy)phenyl)acetamide***



i) ***Cis-2-(3,5-Dimethyl-4-benzenesulphonyl)piperazin-1-yl)-N-(2-methyl-5-(1-(1,1-dimethylethoxycarbonyl)4-piperidinyloxy)phenyl)acetamide***

The subtitle compound was prepared from the product of Example 33 step (ii) (0.42g) and the product of Example 50 step (iii) (0.55g) by the method of Example 33 step (iv).

Purification was by silica gel chromatography eluting with dichloromethane/ethyl acetate (95:5) to give the subtitle compound as colourless gum. Yield: 0.23g

MS: APCI(+ve) 601 (M+1), APCI(-ve) 599 (M-1)

ii) ***Cis-2-(3,5-Dimethyl-4-benzenesulphonyl)piperazin-1-yl)-N-(2-methyl-5-(4-piperidinyloxy)phenyl)acetamide***

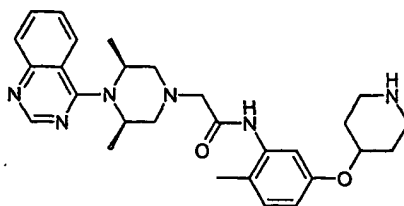
The title compound was prepared from the product of step (i) (0.2g) by the method of Example 27 step (iv) as a white solid after purification by reverse phase HPLC eluting with 1% aq. ammonium acetate/acetonitrile (95% to 60%). Yield: 50mg

MS: APCI(+ve) 501 (M+1), APCI(-ve) 499 (M-1)

<sup>1</sup>H NMR δ (DMSO) 8.8(bs, 1H), 7.8(d, 2H), 7.7(m, 3H), 7.25(s, 1H), 7.15(d, 1H), 6.75(d, 1H), 4.60(m, 1H), 4.2-4.0(bs, 2H), 3.3-3.0(2xm, 4H), 2.2(s, 3H), 2.15-1.70(m, 4H), 1.5(d, 6H)

**Example 52**

***Cis-2-(3,5-Dimethyl-4-(quinazolin-4-yl)piperazin-1-yl)-N-(2-methyl-5-(4-piperidinyloxy)phenyl)acetamide***



**i) 1,1-Dimethylethyl, 4-(4-quinazolinyl)-3,5-dimethylpiperazine-1-carboxylate**

4-Chloroquinazoline (6g), cis-1,1-diethylethyl, 3,5-dimethylpiperazine-1-carboxylate (7.8g), N,N-diisopropylethylamine (32ml) in 1-methyl-2-pyrrolidinone (70ml) were heated at 120 °C for 6 days under nitrogen. The mixture was partitioned between ethyl acetate and brine. The organic phase collected and further washed with brine (x2), collected, dried (MgSO<sub>4</sub>) and solvent evaporated under reduced pressure to leave a pale brown solid. Purification was by silica gel chromatography eluting with ethyl acetate/iso-hexane (3:7) to give the subtitle compound as a pale yellow oil. Yield: 1.1g

MS: APCI(+ve) 343 (M+1)

**ii) cis-4-(4-Quinazolinyl)-2,6-dimethylpiperazine, hydrochloride salt**

The subtitle compound was prepared from the product of step (i) (1g) by the method of Example 27 step (iv) as cream solid. Yield: 1.8g

MS: APCI(+ve) 243 (M+1)

**iii) Cis-2-(3,5-Dimethyl-4-(4-quinazolinyl)piperazin-1-yl)-N-(2-methyl-5-(1-(1,1-dimethylethoxycarbonyl)-4-piperidinyl)oxy)phenyl)acetamide**

The subtitle compound was prepared from the product of step (ii) (0.56g) and the product of Example 50 step (iii) (0.37g) by the method of Example 33 step (iv). Purification was by silica gel chromatography eluting with ethyl acetate/iso-hexane (9:1) to give the subtitle compound as a white solid. Yield: 0.18g

MS: APCI(+ve) 589 (M+1)

iv) ***Cis*-2-(3,5-Dimethyl-4-(quinazolin-4-yl)piperazin-1-yl)-N-(2-methyl-5-(4-piperadinyloxy)phenyl)acetamide**

The title compound was prepared from the product of step (iii) (0.18g) by the method of Example 27 step (iv). Purification was by reverse phase HPLC eluting with 1% aq.

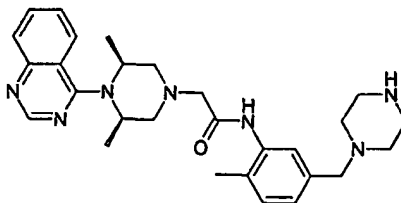
5 ammonium acetate/acetonitrile (99% to 50%) to give the title compound as a white solid.  
Yield: 0.079g

MS: APCI(+ve) 489 (M+1)

<sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>) 9.26(bs, 1H), 9.08(bs, 1H), 8.35(d, 1H), 8.00(d, 1H), 7.95(s, 1H),  
10 7.90(t, 1H), 7.60(t, 1H), 7.10(d, 1H), 6.61(d, 1H), 4.57(m, 1H), 3.25(m+s, 4H), 3.05(m,  
2H), 2.90(d, 2H), 2.60(m, 2H), 2.30(s, 3H), 2.10(m, 2H), 2.0(m, 2H), 1.0(d, 6H)

**Example 53**

***Cis*-2-(3,5-Dimethyl-4-(4-quinazolinyl)piperazin-1-yl)-N-(2-methyl-5-(piperazin-4-yl-methyl)phenyl)acetamide**



i) **2-Chloro-N-5-((1-(1,1-dimethylethoxyxycarbonyl)piperazin-4-yl)methyl)phenyl-2-methyl)acetamide**

The subtitle compound was prepared from the product of Example 27 step (ii) (0.1g) by the  
20 method of Example 33 step (iii) as a beige foam. Yield:0.15g

MS: APCI(+ve) 382 (M+1)

ii) ***Cis*-2-(3,5-Dimethyl-4-(4-quinazolinyl)piperazin-1-yl)-N-(2-methyl-5-(1-(1,1-dimethylethoxyxycarbonyl)piperazin-4-yl-methyl)phenyl)acetamide**

The subtitle compound was prepared from the product of Example 52 step (ii) (0.2g) and the product of step (i) (0.21g) by the method of Example 33 step (iv). Purification was by



silica gel chromatography eluting with ethyl acetate/iso-hexane (9:1) to give the subtitle compound as a white solid. Yield. 0.068g

MS: APCI(+ve) 588 (M+1)

5

**iii) *Cis*-2-(3,5-Dimethyl-4-(4-quinazolinyl)piperazin-1-yl)-N-(2-methyl-5-(piperazin-4-yl-methyl)phenyl)acetamide**

The title compound was prepared from the product of step (ii) (0.069g) by the method of Example 27 step (iv). Purification was by reverse phase HPLC eluting with 1% aq.

10 ammonium acetate/acetonitrile (99% to 50%) to give the title compound as a white solid. Yield: 0.072g

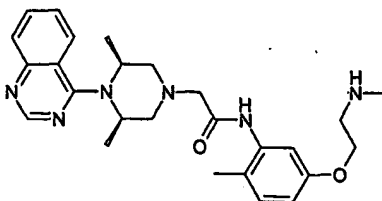
MS: APCI(+ve) 488 (M+1)

<sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>) 8.58(bs, 1H), 8.25(bs, 1H), 7.63(d, 1H), 7.20(m, 2H), 6.95(t, 1H),  
15 6.50(d, 1H), 6.35(d, 1H), 3.60(bs, 2H), 2.80(s, 1H), 2.60(s, 1H), 2.30(bs, 3H), 2.20(d, 1H), 2.0(m, 1H), 1.90(bs, 2H), 1.70(s, 2H), 1.30(bd, 6H)

**Example 54**

***Cis*-2-(3,5-Dimethyl-4-(4-quinazolinyl)piperazin-1-yl)-N-(2-methyl-5-(2-(N-methylamino)ethoxy)phenyl)acetamide**

20



**i) *Cis*-2-(3,5-Dimethyl-4-(4-quinazolinyl)piperazin-1-yl)-N-(2-methyl-5-(2-(1,1-dimethylethoxycarbonyl-N-methylaminoethoxy)phenyl)acetamide**

The subtitle compound was prepared from the product of Example 52 step (ii) (0.64g) and  
25 the product from Example 33 step (iii) (0.59g) by the method of Example 33 step (iv).

Yield. 0.45g

MS: APCI(+ve) 563 (M+1), APCI(-ve) 561 (M-1)

**ii) *Cis*-2-(3,5-Dimethyl-4-(4-quinazolinyl)piperazin-1-yl)-N-(2-methyl-5-(2-(N-methylamino)ethoxy)phenyl)acetamide**

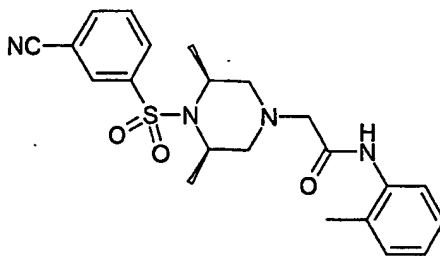
- 5 The title compound was prepared from the product of step (i) (0.4g) by the method of Example 27 step (iv). Purification was by reverse phase HPLC eluting with 1% aq. ammonium acetate/acetonitrile (99% to 50%) to give the title compound as a white solid. Yield: 0.25g

10 MS: APCI(+ve) 463 (M+1)

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 9.30(bs, 1H), 9.12(bs, 1H), 8.39(t, 1H), 8.05(d, 1H), 7.95(m, 2H), 7.60(t, 1H), 7.10(d, 1H), 6.70(d, 1H), 4.20(m, 2H), 4.0(bs, 2H), 3.30(s, 2H), 3.20(m, 2H), 2.90(m, 2H), 2.60(m+s, 5H), 2.35(s, 3H), 1.0(bs, 6H)

15 **Example 55**

***cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide**



20 **i) *cis*-2-(3,5-Dimethylpiperazin-1-yl)-N-(2-methylphenyl)acetamide**

- A mixture of 2-chloro-N-(2-methylphenyl)acetamide (1.83g), N,N-disopropylethylamine (5.0ml), sodium iodide (0.020g) and *cis*-2,6-dimethylpiperazine 1.14g) in ethanol (50ml) was heated at reflux for 2.5 hours. The solvent was removed and the residue was crystallised from ethanol as white needles. It was dissolved in water and the solution was  
25 made basic with 2N aqueous NaOH, extracted with dichloromethane and the extracts were

dried (MgSO<sub>4</sub>), filtered and evaporated to dryness, leaving an oil which crystallised on standing. Yield 1.1g.

<sup>1</sup>H NMR: δ (CDCl<sub>3</sub>) 1.08(6H, d), 1.40(1H br s) 1.94(2H, t), 2.27(3H, s), 2.83(2H, m),

5 2.98(2H, m) 3.14(2H, s), 7.03(1H, m), 7.20(2H, m), 8.18(1H, d), 9.32(1H, br s)

MP: 105-6 °C

ii) *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide

10 The product of step (i) (0.60g), 4-dimethylaminopyridine (0.14g) in pyridine (2.0ml) was stirred while 3-cyanobenzenesulphonyl chloride (0.46g) was added. The mixture was stirred for 10 minutes after which it solidified. After 1 hour the solid was triturated with water and filtered off. It was purified by chromatography on silica eluting with ethyl acetate/iso-hexane (1:1) to give the title compound as a pale yellow solid. Yield: 0.22g.

15

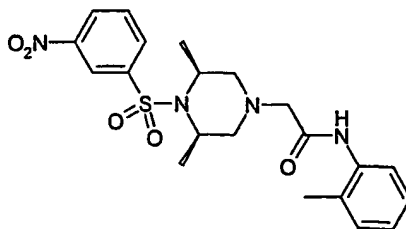
MS: APCI(+ve) 427 (M+1, 100%)

<sup>1</sup>H NMR: δ (CDCl<sub>3</sub>) 1.55(6H, d), 2.17(2H, d of d), 2.32(3H, s), 2.73(2H, d), 3.10(2H, s), 4.13(2H, m), 7.10(1H, m), 7.20(2H, m), 7.67(1H, m), 7.85(1H, m), 7.95(1H, m), 8.05(1H, m), 8.12(1H, m), 8.67(1H, br s).

20 MP: 152-3 °C

### Example 56

*cis*-N-(2-Methylphenyl)-2-[4-(3-nitrobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-acetamide



25

The title compound was prepared from the product of Example 55 step (i) and 3-nitrobenzenesulphonyl chloride by the method of Example 55 step (ii) as an off white solid.

Yield: 3.06g

5

MS: APCI(+ve) 447 (M+1, 100%)

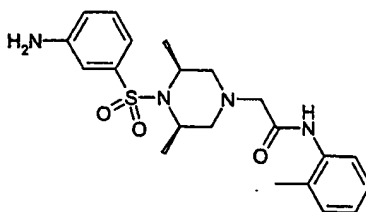
<sup>1</sup>H NMR: δ (CDCl<sub>3</sub>) 1.59(6H, d), 2.20(2H, d of d), 2.30(3H, s), 2.74(2H, d), 3.10(2H, s), 4.16(2H, m), 7.05(1H, m), 7.20(2H, m), 7.75(1H, t), 7.96(1H, d), 8.16(1H, d of d), 8.43(1H, d of d), 8.67(2H, br s).

10 MP: 163-4 °C

### Example 57

*cis*-2-[4-(3-Aminobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide

15

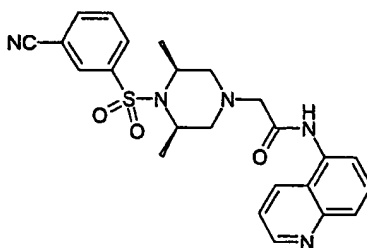


To a stirred solution of the product of Example 56 (3.0g) in ethanol (1500ml) was added 5% palladium on charcoal (1.5g) followed by dropwise addition of hydrazine hydrate (20ml). The mixture was stirred for 1 hour, filtered through 'hyflo' and the filtrate was  
20 evaporated to dryness. The solid residue was crystallised from ethanol to give the title compound as a white solid. Yield 1.6g.

MS: APCI(+ve) 417 (M+1, 100%)

<sup>1</sup>H NMR: δ (CDCl<sub>3</sub>) 1.54(6H, d), 2.18(2H, d of d), 2.30(3H, s), 2.65(2H, d), 3.07(2H, s),  
25 3.90(2H, s), 4.15(2H, m), 6.82(1H, d of d), 7.05-7.20(6H, m), 7.99(1H, d), 8.75(1H, s).

MP: 202-3 °C

**Example 58*****Cis-2-(3,5-Dimethyl-4-(3-cyanobenzenesulphonyl)piperazin-1-yl)-N-(quinolin-5-yl)acetamide*****i) *Cis-2-(3,5-Dimethyl-piperazin-1-yl)-N-(quinolin-5-yl)acetamide***

A mixture of 2-chloro-N-(quinolin-5-yl)acetamide (7.76g) (J. Indian Chem Soc, 1940, 17, 619-621), cis-2,6-dimethylpiperazine (4.42g), sodium bicarbonate (8.9g) in ethanol (100ml) was heated at reflux for 4h. The solvent was removed under reduced pressure.

The residue was partitioned between chloroform and brine. The organic phase collected and the aqueous phase further extracted (x6) with chloroform. The combined extracts dried (MgSO<sub>4</sub>) and solvent removed under reduced pressure. Yield: 6.8g

MS: APCI(+ve) 299 (M+1)

**ii) *Cis-2-(3,5-Dimethyl-4-(3-cyanobenzenesulphonyl)piperazin-1-yl)-N-(quinolin-5-yl)acetamide***

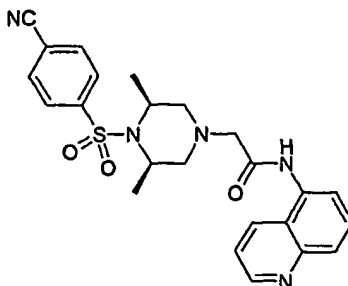
The product from step (i) (150mg), 4-N,N-dimethylaminopyridine (31mg) in pyridine (0.5ml) was treated in one portion with 3-cyanobenzenesulphonyl chloride (1eq) and then immediately heated for 30 minutes. The mixture was partitioned between dichloromethane and water. The organic phase collected, dried (MgSO<sub>4</sub>) and solvent removed under reduced pressure. The residue was purified by reverse phase HPLC eluting with 0.1% aq. ammonium acetate/acetonitrile (95% to 50%) as eluant to give the title compound as a white solid. Yield: 8mg

MS: APCI(+ve) 464 (M+1)

$^1\text{H}$ NMR  $\delta$  ( $\text{CD}_3\text{OD}$ ) 9.87(d, 1H), 8.4(d, 1H), 8.3(d, 1H), 8.2(m, 2H), 8.0(m, 2H), 7.78(m, 2H), 7.6(m, 1H), 4.2(m, 2H), 3.24(s, 2H), 2.82(d, 2H), 2.1(dd, 2H), 1.57(d, 6H)

### Example 59

5 ***Cis*-2-(3,5-Dimethyl-4-(4-cyanobenzenesulphonyl)piperazin-1-yl)-N-(quinolin-5-yl)acetamide**



The title compound was prepared from the product of Example 58 step (i) (0.503 mmol) and 4-cyanobenzenesulphonyl chloride (0.503mmol) by the method of Example 58 step (ii)  
10 as a white solid. Yield: 4mg

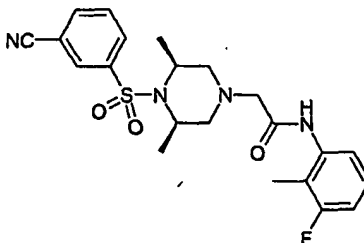
MS: APCI(+ve) 464 (M+1)

$^1\text{H}$ NMR  $\delta$  ( $\text{CD}_3\text{OD}$ ) 8.9(d, 1H), 8.4(d, 1H), 8.1(d, 2H), 7.93-7.96(m, 2H), 7.8(m, 2H), 7.6(m, 1H), 4.2(m, 2H), 3.24(s, 2H), 2.81(d, 2H), 2.1(dd, 2H), 1.57(d, 6H)

15

### Example 60

***Cis*-2-(4-(3-cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl)-N-(3-fluoro-2-methylphenyl)acetamide**



20 **i) *cis*-(3,5-Dimethylpiperazin-1-yl)-N-(2-methyl-3-fluorophenyl)acetamide**

The subtitle compound was prepared from the product of Example 36 step (i) (14.5g) and *cis*-2,6-dimethylpiperazine (9.0g) by the method of Example 58 step (i) as cream solid.

Yield: 11.48g

5 MS: APCI(+ve) 280 (M+1)

**ii) *Cis*-2-(4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl)-N-(3-fluoro-2-methylphenyl)acetamide**

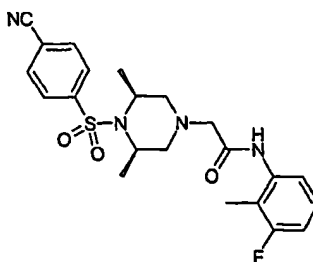
The title compound was prepared from the product of step (i) (0.503mmol) and 3-cyanobenzenesulphonyl chloride (0.503mmol) by the method of Example 58 step (ii) as a white solid. Yield: 44mg

MS: APCI(+ve) 445 (M+1)

<sup>1</sup>H NMR  $\delta$  (CD<sub>3</sub>OD) 8.24(d, 1H), 8.14(d, 1H), 7.98(d, 1H), 7.76(t, 1H), 7.36(d, 1H), 7.1(q, 1H), 6.93(t, 1H), 4.14-4.16(m, 2H), 3.10(s, 2H), 2.73(d, 2H), 2.16(d, 3H), 2.04(dd, 2H), 1.53(d, 6H)

**Example 61**

***Cis*-2-(4-(4-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl)-N-(3-fluoro-2-methylphenyl)acetamide**



The title compound was prepared from the product of Example 60 step (i) (0.503mmol) and 4-cyanobenzenesulphonyl chloride (0.503mmol) by the method of Example 58 step (ii) as a white solid. Yield: 4mg

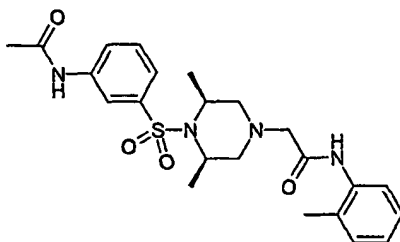
25

MS: APCI(+ve) 445 (M+1)

<sup>1</sup>H NMR δ (CD<sub>3</sub>OD) 8.24(d, 1H), 8.14(d, 1H), 7.98(d, 1H), 7.76(t, 1H), 7.36(d, 1H), 7.1(q, 1H), 6.93(t, 1H), 4.14–4.16(m, 2H), 3.10(s, 2H), 2.73(d, 2H), 2.16(d, 3H), 2.04(dd, 2H), 1.53(d, 6H)

5 **Example 62**

***cis*-2-[4-(3-Acetylaminobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide**



A solution of the product from Example 57 (0.2g) and N,N-diisopropylethylamine (0.3ml) in dichloromethane (10ml) was rapidly stirred whilst a solution of acetyl chloride (0.055g) in dichloromethane (2.0ml) was added. After 3 hours a further amount of acetyl chloride (0.022g) was added, the mixture was stirred 3 hours more then evaporated to dryness. The residue was triturated with water, filtered and dried *in vacuo*, to give the title compound as a white solid. Yield 0.17g.

15

MS: APCI(+ve) 459 (M+1, 100%)

<sup>1</sup>H NMR: δ (CDCl<sub>3</sub>+DMSO) 1.53(6H, d), 2.17(3H, s), 2.26(2H, m), 2.30(3H, s), 2.66(2H, d), 3.08(2H, s), 4.14(2H, m), 7.07(1H, m), 7.20(2H, m), 7.42(1H, m), 7.48(1H, m), 7.82(1H, d), 7.95(1H, d), 8.16(1H, s), 8.77(1H, s), 9.49(1H, s)

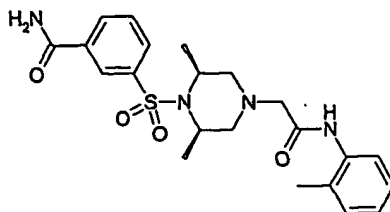
20 MP: 236-8 °C

**Example 63**

***cis*-2-[4-(3-Aminocarbonylbenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide**

25





Hydrgen chloride gas was bubbled through a solution of the product of Example 55 step (ii) (0.21g), in methanol (50ml) at 0°C for 4 hours. The mixture was evaporated to dryness, the residue was dissolved in methanol and ethylenediamine (0.18g) was added.

- 5 After 3 hours LC/MS indicated mainly amide. After 18 hours the mixture was evaporated to dryness, the residue was triturated with ether/ethanol, filtered and the solid was purified by chromatography on silica gel eluting with dichloromethane containing ethanol (2.5-5%) to give the title compound as a white solid. Yield 0.08g.

10 MS: APCI(+ve) 445 (M+1, 100%)

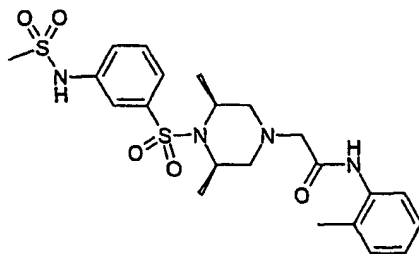
<sup>1</sup>H NMR: δ (CDCl<sub>3</sub>+DMSO) 1.54(6H, d), 2.13(2H, m), 2.29(3H, s), 2.70(2H,d), 3.06(2H, s), 4.14(2H, m), 6.24(1H, br s), 7.07(1H, m), 7.21(2H, m), 7.60(1H, t), 7.68(1H, br s), 7.93(2H, d), 8.15(1H, d), 8.41(1H, s), 8.74(1H, s)

MP: 124-5 °C

15

#### Example 64

*cis*-2-[4-(3-Methanesulphonylaminobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide



- 20 The title compound was prepared from the product of Example 57 and methane sulphonyl chloride by the method of Example 62. The solid obtained at the end of the reaction was suspended in ethanol (50ml) to which a solution of K<sub>2</sub>CO<sub>3</sub> (0.2g) in water (10ml) was added, and stirred for 18 hours, in order to hydrolyse any bis-sulphonamide. The ethanol

was removed, water (50ml) was added and the pH was adjusted to 5.0. The solid was filtered off, washed with water and ether and dried *in vacuo* to give the title compound as a white solid. Yield 0.13g.

5 MS: APCI(+ve) 495 (M+1, 100%)

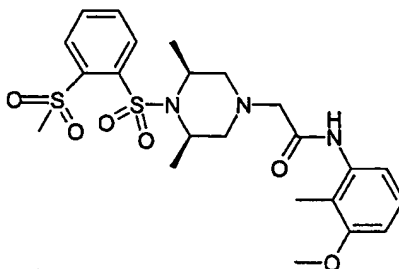
<sup>1</sup>H NMR:  $\delta$  (CDCl<sub>3</sub>) 1.54(6H, d), 2.20(2H, m), 2.30(3H, s), 2.68(2H, d), 3.06(3H, s), 3.09(2H, s), 4.13(2H, m), 7.07(1H, m), 7.20(2H, m), 7.25(1H, s), 7.40(1H, d of d), 7.48(1H, t), 7.60(1H, d), 7.68(1H, m), 7.95(1H, d), 8.73(1H, s)

MP: 102-3 °C

10

#### Example 65

***cis*-2-[4-(2-Methanesulphonylbenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(3-methoxy-2-methylphenyl)acetamide**



15 i) ***cis*-[3,5-Dimethylpiperazin-1-yl]-N-(3-methoxy-2-methylphenyl)acetamide**

The subtitle compound was prepared from 2-chloro-N-(3-methoxy-2-methylphenyl)acetamide (10.72g) and *cis*-2,6-dimethylpiperazine (6.29g) by the method of Example 58 step (i) as a tan solid. Yield: 13.13g

20 <sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>) 9.32(bs, 1H), 7.79(d, 1H), 7.18(t, 1H), 6.68(d, 1H), 3.83(s, 3H), 3.14(s, 2H), 2.93-3.04(m, 2H), 2.81-2.85(m, 2H), 2.14(s, 3H), 1.92(t, 2H), 1.10(d, 6H)

ii) ***cis*-2-[4-(2-Methanesulphonylbenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(3-methoxy-2-methylphenyl)acetamide**

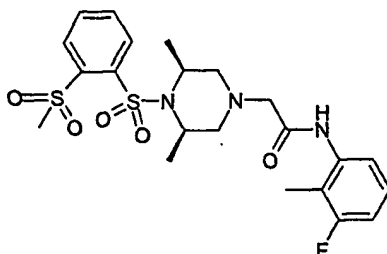
The title compound was prepared from the product of step (i) (0.503mmol) and 2-methanesulphonylbenzenesulphonyl chloride (0.503mmol) by the method of Example 58 step (ii) as a white solid. Yield: 6mg

5 MS: APCI(+ve) 510(M+1)

<sup>1</sup>H NMR δ (CD<sub>3</sub>OD) 8.4(m, 1H), 8.3(m, 1H), 7.91-7.89(m, 2H), 7.16-7.18(m, 2H), 6.8(t, 1H), 4.2(m, 2H), 3.84(s, 3H), 3.43(s, 3H), 3.14(s, 2H), 2.74(d, 2H), 2.33(dd, 2H), 2.14(s, 3H), 1.61(d, 6H)

10 **Example 66**

*cis*-2-[4-(2-Methanesulphonylbenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(3-fluoro-2-methylphenyl)acetamide



The title compound was prepared from the product of Example 60 step (i) (0.503mmol) and 2-methanesulphonylbenzenesulphonyl chloride (0.503mmol) by the method of Example 58 step (ii) as a white solid. Yield: 17mg

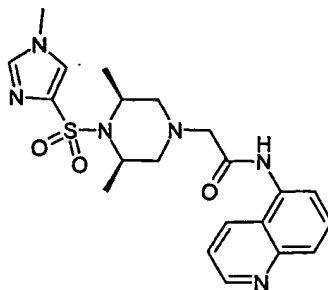
MS: APCI(+ve) 498 (M+1)

<sup>1</sup>H NMR δ (CD<sub>3</sub>OD) 8.4(m, 1H), 8.3(m, 1H), 7.89-7.91(m, 2H), 7.4(d, 1H), 7.1(q, 1H), 6.9(t, 1H), 4.2(m, 2H), 3.44(s, 3H), 3.16(s, 2H), 2.74(d, 2H), 2.3(dd, 1H), 2.20(d, 2H), 1.62(d, 6H)

**Example 67**

*cis*-2-[4-(1-Methylimidazol-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide

91.



The title compound was prepared from the product of Example 58 step (i) (0.503mmol) and 1-methylimidazole-4-sulphonyl chloride (0.503mmol) by the method of Example 58 step (ii) as a white solid. Yield: 16mg

5

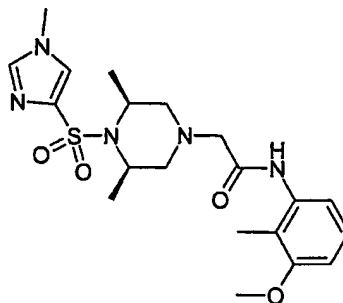
MS: APCI(+ve) 443 (M+1)

$^1\text{H}$  NMR  $\delta$  ( $\text{CD}_3\text{OD}$ ) 8.90(d, 1H), 4.45(d, 1H), 7.97(t, 1H), 7.82(s, 1H), 7.80(d, 1H), 7.68(s, 1H), 7.58-7.63(m, 1H), 4.17-2.21(m, 2H), 3.79(s, 3H), 3.26(s, 2H), 2.80(d, 2H), 2.25(dd, 2H), 1.58(d, 6H)

10

### Example 68

*cis*-2-[4-(1-Methylimidazol-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-(3-methoxy-2-methylphenyl)acetamide



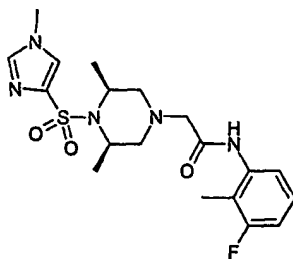
15 The title compound was prepared from the product of Example 65 step (i) (0.503mmol) and 1-methylimidazol-4-sulphonyl chloride (0.503mmol) by the method of Example 58 step (ii) as a white solid. Yield: 31mg

MS APCI(+ve) 436 (M+1)

<sup>1</sup>H NMR δ (CD<sub>3</sub>OD) 7.77 (s, 1H), 7.67(s, 1H), 7.16-7.18(m, 2H), 6.82-6.85(m, 1H), 4.14-4.18(m, 2H), 3.84(s, 3H), 3.79(s, 3H), 3.10(s, 2H), 2.72(d, 2H), 2.20(dd, 2H), 2.13(s, 3H), 1.53(d, 6H)

5 **Example 69**

*cis*-2-[4-(1-Methylimidazol-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-(3-fluoro-2-methylphenyl)acetamide



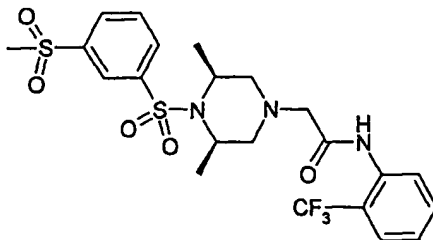
The title compound was prepared from the product of Example 60 step (i) (0.503mmol)  
10 and 1-methylimidazol-4-sulphonyl chloride (0.503mmol) by the method of Example 58  
step (ii) as a white solid. Yield: 21mg

MS: APCI(+ve) 424 (M+1)

<sup>1</sup>H NMR δ (CD<sub>3</sub>OD) 7.77 (s, 1H), 7.67 (s, 1H), 7.43 (d, 1H), 7.20(q, 1H), 6.95(t, 1H), 4.12-  
15 4.20(m, 2H), 3.79(s, 3H), 3.12(s, 2H), 2.72(d, 2H), 2.17-2.23(m, 5H), 1.54(d, 6H)

**Example 70**

*cis*-2-[4-(3-Methanesulphonylbenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-trifluoromethylphenyl)acetamide



20

i) 2-Chloro-N-(2-trifluoromethylphenyl)acetamide

The subtitle compound was prepared from 2-trifluoromethylaniline(10.5g) and chloroacetyl chloride (6.8ml) by the method of Example 33 step (iii) as a white solid.

Yield: 13.7g

5 MS: APCI(-ve) 236 (M-1)

**ii) *cis*-3,5-Dimethylpiperazin-1-yl]-N-(2-trifluoromethylphenyl)acetamide**

The subtitle compound was prepared from the product of step (i) (7.6g ) and *cis*-2,6-dimethylpiperazine (3.53g) by the method of Example 58 step (i)

10 as a white solid. Yield: 8.57g

MS: APCI(+ve) 316 (M+1)

**15 iii) *cis*-2-[4-(3-Methanesulphonylbenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-trifluoromethylphenyl)acetamide**

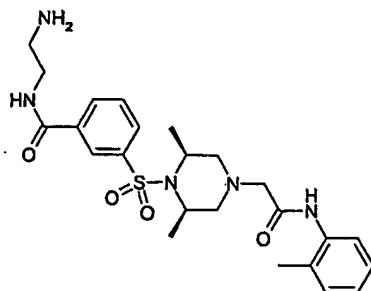
The product of step (iii) (0.25g) and 3-methanesulphonylbenzenesulphonyl chloride (0.606g), potassium carbonate (0.275g) in 2,6-lutidine(0.5ml) were heated in a 100Watt microwave oven at 120 °C for 10min. The mixture was then partitioned between dichloromethane and water. The organic phase collected, dried (MgSO<sub>4</sub>), and the solvent  
20 evaporated under reduced pressure. Purification was by reverse phase HPLC eluting with 1% aq. ammonium acetate/acetonitrile (95% to 60%) to give the title compound as a white solid. Yield: 0.1g

MS: APCI(+ve) 534 (M+1)

25 <sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 9.16(bs, 1H), 8.41(s, 1H), 8.30(d, 1H), 8.20(d, 1H), 7.58(t, 1H), 7.26(d, 1H), 4.15(m, 2H)

**Example 71**

***cis*-2-[4-(2-Aminoethylaminocarbonylbenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-  
30 N-(2-methylphenyl)acetamide**



The title compound was prepared from the product of Example 55 by the method of Example 63 followed by addition of ethylenediamine, the mixture was heated at reflux for 5 hours, evaporated to dryness and the residue was crystallised from ethanol to give the title compound as a white solid. Yield 0.15g

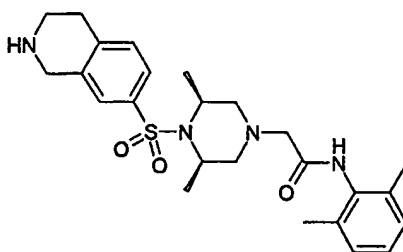
MS: APCI(+ve) 488 (M+1, 100%)

<sup>1</sup>H NMR:  $\delta$  (CDCl<sub>3</sub>) 1.56(8H, m), 2.17(2H, m), 2.29(3H, s), 2.68(2H, d), 2.98(2H, t), 3.06(2H, s), 3.51(2H, m), 4.14(2H, m), 6.97(1H, br t), 7.07(1H, m), 7.20(2H, m), 7.60(1H, t), 7.9(3H, m), 8.25(1H, m), 8.71(1H, br s)

MP: 90-2 °C

#### Example 72

*cis*-2-[4-(1,1,2,2-Tetrahydroisoquinilin-7-sulphonyl-7-yl)-3,5-dimethylpiperazin-1-yl]-N-(2,6-dimethylphenyl)acetamide



i) *cis*-3,5-Dimethylpiperazin-1-yl]-N-(2,6-dimethylphenyl)acetamide

The subtitle compound was prepared from 2-chloro-N-(2,6-dimethylphenyl)acetamide (6.54g) and *cis*-2,6-dimethylpiperazine (3.78g) by the method of Example 58 step (i) as a white solid. Yield: 7.85g

MS: APCI(+ve): 276(M+1)

ii) *cis*-2-[4-(N-Trifluoroacetyl(1,1,2,2-tetrahydroisoquinilin)-7-sulphonyl-7-yl)-3,5-dimethylpiperazin-1-yl]-N-(2,6-dimethylphenyl)acetamide

The subtitle compound was prepared from the product of step (i) (0.165g) and N-trifluoroacetyl(1,1,2,2-tetrahydroisoquinolin)-7-sulphonyl chloride (0.39g) by the method of Example 58 step (ii) as a white solid. Yield: 96mg

MS: APCI(+ve) 567 (M+1)

iii) *cis*-2-[4-(1,1,2,2-Tetrahydroisoquinilin-7-sulphonyl-7-yl)-3,5-dimethylpiperazin-1-yl]-N-(2,6-dimethylphenyl)acetamide

The product from step (ii) (90mg), potassium carbonate (200mg) in water (10ml) and methanol (15ml) were heated at reflux for 2h. Water (50ml) was added and the mixture extracted with ethyl acetate. The organic phase collected, dried (MgSO<sub>4</sub>) and solvent evaporated under reduced pressure to give the title compound as a white solid. Yield: 55mg

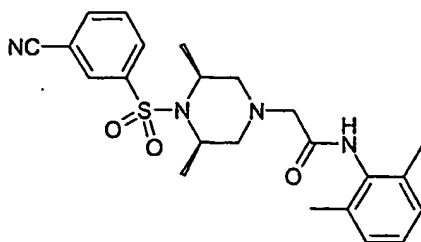
MS: APCI(+ve) 471 (M+1)

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 8.29(s, 1H), 7.55(d, 1H), 7.50(s, 1H), 7.17(d, 1H), 7.11(m, 3H), 4.14(m, 2H), 4.06(s, 2H), 3.48(q, 1H), 3.17(t, 1H), 3.12(s, 2H), 2.87(t, 2H), 2.72(d, 2H), 2.25(d, 1H), 2.22(s, 6H), 2.05(s, 1H), 1.69(bs, 1H), 1.51(d, 6H), 1.19-1.28(m, 4H)

**Example 73**

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2,6-dimethylphenyl)acetamide





The title compound was prepared from the product of Example 72 step (i) (0.165g) and 3-cyanobenzenesulphonyl chloride (0.15g) by the method of Example 58 step (ii) as a white solid. Yield: 40mg

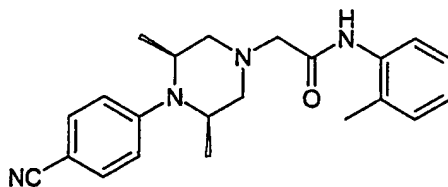
5

MS: APCI(+ve) 441 (M+1)

<sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>) 8.22 (s, 1H), 8.13(s, 1H), 8.05(d, 1H), 7.86(d, 1H), 7.67(t, 1H), 7.12(m, 3H), 4.15(m, 2H), 3.14(s, 2H), 2.78(d, 2H), 2.22(s, 8H), 1.54(d, 6H)

#### 10 Example 74

*cis*-2-[4-(4-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide



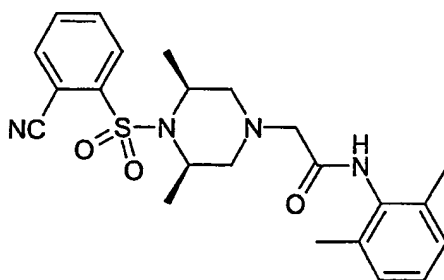
15 4-Cyanobenzenesulphonyl chloride (0.36g) was added to a stirred mixture of the product of Example 55 step (i) (0.5g) and potassium carbonate (0.62g) in 1-methyl-2-pyrrolidinone (3ml). After 20 min the reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with water and brine, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. Purification was by flash chromatography eluting with 1% ethanol in  
20 dichloromethane followed by trituration with methanol to give the title compound as a white crystalline solid. Yield 55mg.

MS: ES (+ve) 427 (M+1)

$^1\text{H}$  NMR:  $\delta$  ( $\text{CDCl}_3$ ) 8.67 (1H, brs), 7.99-7.93 (3H, m), 7.83 (2H, d), 7.21 (2H, m), 7.08 (1H, m), 4.14 (2H, m), 3.10 (2H, s), 2.73 (2H, d), 2.30 (3H, s), 2.18 (2H, dd), 1.57 (3H, s), 1.54 (3H, s).

5 **Example 75**

*cis*-2-[4-(2-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2,6-dimethylphenyl)acetamide, hydrochloride salt



10 The free base of the title compound was prepared from the product of Example 72 step (i) (0.165g) and 2-cyanobenzenesulphonyl chloride (0.15g) by the method of Example 58 step (ii). The title compound was prepared by adding 1M hydrogen chloride in diethyl ether to a solution of the free base to produce a white precipitate. This was filtered and further washed with diethyl ether to give the title compound as a white solid. Yield: 20mg

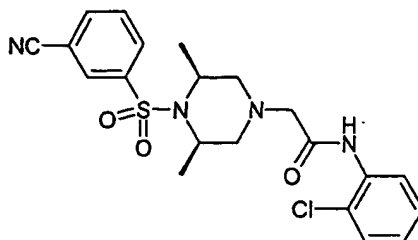
15

MS: APCI(+ve) 441 ( $M+1$ )

$^1\text{H}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 8.19(bs, 1H), 7.91(bs, 1H), 7.78(bs, 2H), 7.10(m, 3H), 4.40(bs, 2H), 4.20(bs, 2H), 3.50(m, 3H), 2.20(s, 6H), 2.00-1.40(m, 6H)

20 **Example 76**

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-chlorophenyl)acetamide



The title compound was prepared from the product of Example 15 step (ii) (0.2g) and 3-cyanobenzenesulphonyl chloride (0.28g) by the method of Example 74 as a white solid. Yield 8mg.

5

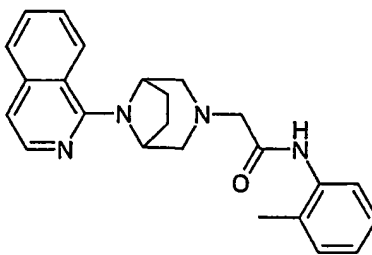
MS: APCI (+ve) 447 (M+1)

<sup>1</sup>H NMR:  $\delta$  (CDCl<sub>3</sub>) 9.45 (1H, brs), 8.49 (1H, dd), 8.13 (1H, s), 8.05 (1H, d), 7.87 (1H, d), 7.68 (1H, t), 7.38 (1H, d), 7.29 (1H, m), 7.06 (1H, t), 4.14 (2H, m), 3.11 (2H, s), 2.72 (2H, d), 2.18 (1H, dd), 1.60 (3H, s), 1.58 (3H, s).

10

#### Example 77

2-[8-(Isquinolin-1-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide



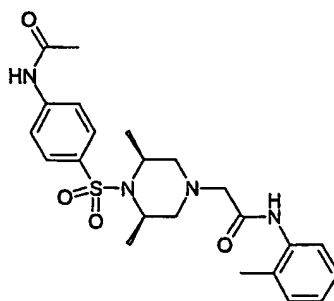
15 The title compound was prepared from the product Example 20 step (iv) (0.32g) and 1-chloroisoquinoline (0.14g) by the method of Example 52 step (i) as a beige solid. Yield: 40mg

MS: ESI(+ve) 387 (M+1)

20 <sup>1</sup>H NMR  $\delta$  (DMSO) 9.21(bs, 1H), 8.20(d, 1H), 8.00(d, 1H), 7.93(d, 2H), 7.70(t, 1H), 7.60(t, 1H), 7.35(d, 1H), 7.20(m, 2H), 7.06(t, 1H), 4.40(bs, 2H), 2.98(d, 2H), 2.85(d, 2H), 2.30(s, 3H), 2.00(d, 2H), 1.90(m, 2H)

**Example 78**

***cis*-2-[4-(4-Acetamidobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide**



5

2,6-Lutidine (0.3ml) was added to a mixture of 4-acetamidobenzenesulphonyl chloride (0.25g), potassium carbonate (0.18g) and the product of Example 55 step (i) (0.14g). The reaction mixture was heated at 100°C for 5 minutes in a 100 Watt microwave oven, allowed to cool and partitioned between dichloromethane and water. The organic phase was washed with brine, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. Purification was by reverse phase HPLC (acetonitrile/ 1% aq.ammonium acetate). Yield 15mg.

10

MS: AP (+ve) 459 (M+1)

<sup>1</sup>H NMR: δ (DMSO) 10.35 (1H,s), 7.76 (4H,q), 7.55 (1H,d), 7.22-7.14 (2H,m), 7.07

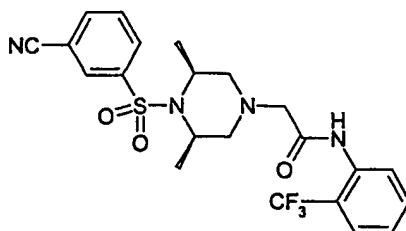
15

(1H,m), 4.00 (2H,m), 3.02 (2H,s), 2.64 (2H,d), 2.20 (3H,s), 2.09 (3H,s), 1.92 (2H,dd), 1.42 (3H,s), 1.40 (3H,s)

**Example 79**

***cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-trifluoromethylphenyl)acetamide**

20



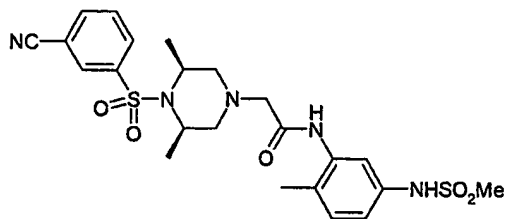
The title compound was prepared from the product of Example 70 step (i) (0.189g) and 3-cyanobenzenesulphonyl chloride (0.15g) by the method of Example 58 step (ii) as a white solid. Yield: 17mg

5 MS: APCI(+ve) 481 (M+1)

<sup>1</sup>H NMR δ (DMSO) 8.98(bs, 1H), 8.11(m, 2H), 7.93(m, 2H), 7.05(m, 4H), 4.10(m, 2H), 3.30(s, 2H), 2.90(d, 2H), 2.40(bd, 2H), 1.50(d, 6H)

### Example 80

10 ***cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-methanesulphonamidophenyl)acetamide**



i) ***cis*-1-(3-Cyanobenzenesulphonyl)-2,6-dimethyl-4-phenylmethylpiperazine**

A solution of *cis*-4-benzyl-2,6-dimethylpiperazine (1g), 4-N,N-dimethylaminopyridine(0.54g), 3-cyanobenzenesulphonyl chloride (2.13g) in pyridine  
15 (3ml) were stirred at ambient temperature. After 1h the mixture was partitioned between dichloromethane and water. The organic phase further washed with brine, collected, dried, (MgSO<sub>4</sub>) and solvent evaporated under reduced pressure to leave the subtitle compound as an orange gum. Yield: 1g

20

MS: APCI(+ve) 370 (M+1)

ii) ***cis*-1-(3-Cyanobenzenesulphonyl)-2,6-dimethylpiperazine**

A solution of the product from step (i) (1g) in 1,2-dichloroethane (10ml) was treated with  
25 1-chloroethyl chloroformate (0.44ml). The mixture was heated at 80 °C for 16h.

The solvents were then evaporated under reduced pressure and the residue dissolved in methanol (50ml). The mixture then heated at 50 °C for 1h. The solvents were then

evaporated under reduced pressure. Purification was by trituration with ethyl acetate and filtration to give the subtitle compound as a white solid. Yield: 0.85g

MS: APCI(+ve) 279 (M+1)

5

**iii) *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-bis(methanesulphonyl)amidophenyl)acetamide**

A solution of the product from step (ii) (0.5g) and the product of Example 24 step (i) (0.8g), N,N-diisopropylethylamine (0.6ml), potassium iodide (2mg) in 1-methyl-2-pyrrolidinone (10ml) were heated at 90 °C for 3h. The mixture was then partitioned dichloromethane and water. The organic phase collected, further washed with brine, dried (MgSO<sub>4</sub>) and solvent evaporated under reduced pressure to give the subtitle compound as a brown foam.

Yield: 1.04g

15

MS: APCI(+ve) 597 (M+1)

**iv) *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-methanesulphonamidophenyl)acetamide**

The product from step (iii) (1g), potassium carbonate (1g), water (10ml) and tetrahydrofuran (20ml) were stirred at ambient temperature for 16h then heated at 90 °C for 6h. The mixture partitioned between dichloromethane and water. The organic phase collected, dried (MgSO<sub>4</sub>) and solvent evaporated under reduced pressure.

Purification was by silica gel chromatography eluting with iso-hexane/ethyl acetate (1:9) to give the title compound as a white solid. Yield: 0.5g

25

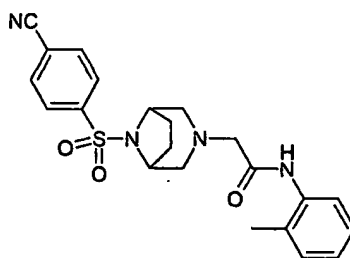
MS: APCI(+ve) 520(M+1), APCI(-ve) 518 (M-1)

<sup>1</sup>HNMR δ (CDCl<sub>3</sub>) 8.9(bs, 1H), 8.13(2xs, 2H), 8.05(d, 1H), 7.90(d, 1H), 7.70(t, 1H), 7.40(bs, 1H), 7.10(m, 2H), 4.10(m, 2H), 3.10(s, 2H), 2.95(s, 3H), 2.70(d, 2H), 2.30(s, 3H), 2.20(m, 2H), 1.60(d, 6H)

30

**Example 81**

**2-[8-(4-Benzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide**



5

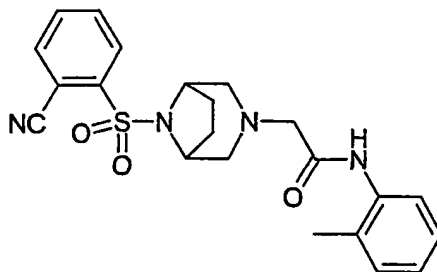
The title compound was prepared from the product of Example 20 step (iv) (0.34mmol) and 4-cyanobenzenesulphonyl chloride (0.34mmol) by the method of Example 58 step (ii) as a white solid. Yield: 10mg

10 MS: ESI(+ve) 425 (M+1)

<sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>) 8.68(bs, 1H), 8.05(m, 3H), 7.83(d, 2H), 7.23-7.17(m, 2H), 7.07(m, 1H), 4.26(m, 2H), 3.19(s, 2H), 2.86(dd, 2H), 2.65(d, 2H), 2.27(s, 3H), 1.94(m, 2H), 1.74(m, 2H)

15 **Example 82**

**2-[8-(2-Benzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide**



The title compound was prepared from the product of Example 20 step (iv) (0.34mmol) and 2-cyanobenzenesulphonyl chloride (0.34mmol) by the method of Example 58 step (ii) as a white solid. Yield: 8mg

20

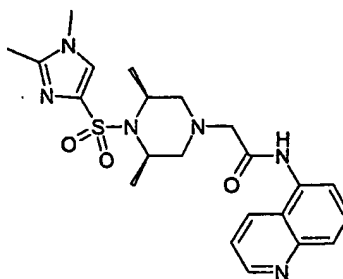
MS: APCI(+ve) 425 (M+1)

<sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>) 8.77(bs, 1H), 8.15(dd, 1H), 8.03(d, 1H), 7.88(ss, 1H), 7.78-7.69(m, 2H), 7.25-7.18(m, 2H), 7.07(t, 1H), 4.36(m, 2H), 3.20(s, 3H), 2.85(dd, 1H), 2.74(d, 1H), 2.30(s, 3H), 2.07-1.99 (m, 4H)

5

### Example 83

*cis*-2-[4-(1,2-Dimethylimidazol-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide



- 10 The title compound was prepared from the product of Example 58 step (i) (0.503mmol) and 1,2-dimethylimidazole-4-sulphonyl chloride (0.503mmol) by the method of Example 58 step (ii) as a white solid. Yield: 20mg

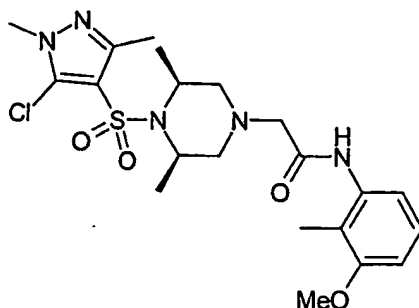
MS: APCI(+ve) 457 (M+1)

- 15 <sup>1</sup>H NMR  $\delta$  (CD<sub>3</sub>OD) 8.88-8.89(m, 1H), 8.44(d, 1H), 7.97-7.94(m, 1H), 7.76-7.81(m, 2H), 7.56-7.60(m, 2H), 4.19-4.13(m, 2H), 3.65(s, 3H), 3.25(s, 2H), 2.79(d, 2H), 2.38(s, 3H), 2.54(dd, 2H), 1.55(d, 6H)

### Example 84

- 20 *cis*-2-[4-(5-Chloro-1,3-dimethylpyrazole-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-(3-methoxy-2-methylphenyl)acetamide





The title compound was prepared from the product of Example 65 step (i) (0.503mmol) and 5-chloro-1,3-dimethyl-4-sulphonyl chloride (0.503mmol) by the method of Example 58 step (ii) as a white solid. Yield: 6mg

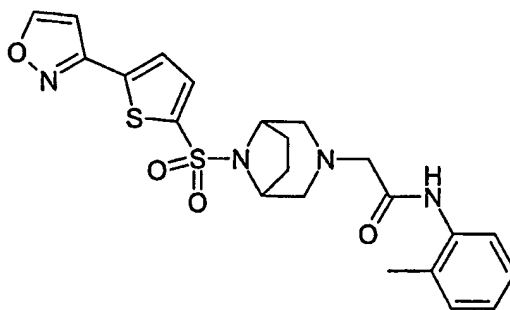
5

MS: APCI(+ve) 485 (M+1)

<sup>1</sup>H NMR  $\delta$  (CD<sub>3</sub>OD) 7.15-7.16(m, 2H), 6.81-6.84(m, 1H), 4.07-4.10(m, 2H), 3.83(s, 3H), 3.82(s, 3H), 3.15(s, 2H), 2.79(d, 2H), 2.37(s, 3H), 2.56(dd, 2H), 2.12(s, 3H), 1.54(d, 6H)

#### 10 Example 85

2-[8-(2-(Isoxazol-3-yl)thiophen-5-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide



The title compound was prepared from the product of Example 20 step (iv) (0.34mmol) and 2-(isoxazol-3-yl)thiophenesulphonyl chloride (0.34mmol) as a white solid. Yield: 10mg

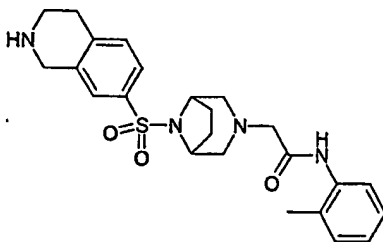
15

MS: ESI(+ve) 473 (M+1)

$^1\text{H}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 8.72(bs, 1H), 8.05(d, 1H), 7.61(d, 1H), 7.46(d, 1H), 7.23(d, 2H), 7.06(t, 1H), 6.53(d, 1H), 4.33(m, 2H), 3.22(s, 2H), 2.89(dd, 2H), 2.73(d, 2H), 2.28(s, 3H), 1.94(m, 2H), 1.87(m, 2H)

5 **Example 86**

**2-[8-(1,1,2,2-Tetrahydroisoquinilin-7-sulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide**



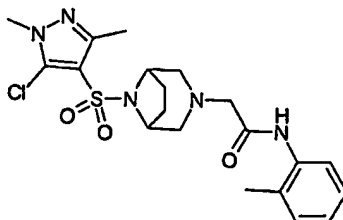
10 The title compound was prepared from the product of Example 20 step (iv) (0.34mmol) and N-trifluoroacetyl-1,1,2,2-tetrahydroisoquinoline-7-sulphonyl chloride (0.34mmol) by the method of Example 58 step (ii) followed by the method of Example 72 step (iii) as a white solid. Yield: 26mg

15 MS: ESI(+ve) 551 (M+1)

$^1\text{H}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 8.73(bs, 1H), 8.04(d, 1H), 7.77-7.68(m, 2H), 7.33(t, 1H), 7.25-7.17(m, 2H), 7.06(t, 1H), 4.83(d, 2H), 4.24(m, 2H), 3.92(dt, 2H), 3.19(s, 2H), 3.05(m, 2H), 2.85(dd, 2H), 2.66(d, 2H), 2.27(s, 3H), 1.90(m, 2H), 1.76(d, 2H)

20 **Example 87**

**cis-2-[4-(5-Chloro-1,3-dimethylpyrazole-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide**



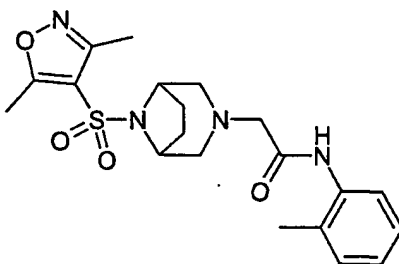
The title compound was prepared from the product of Example 20 step (iv) (0.34mmol) and 5-chloro-1,3-dimethylpyrazole-4-sulphonyl chloride (0.34mmol) by the method of Example 58 step (ii) as a white solid. Yield: 12mg

5 MS: ESI (+ve) 452 (M+1)

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 8.77(bs, 1H), 8.04(d, 1H), 7.23-7.18(m, 2H), 7.07(t, 1H), 4.25(m, 2H), 3.83(s, 3H), 3.19(s, 2H), 2.85(dd, 2H), 2.65(d, 2H), 2.43(s, 3H), 2.30(s, 3H), 1.95(s, 4H)

### Example 88

10 *cis*-2-[4-(3,5-Dimethylisoxazole-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide



The title compound was prepared from the product of Example 20 step (iv) (0.34mmol) and 3,5-dimethylisoxazole-4-sulphonyl chloride (0.34mmol) by the method of Example 58  
15 step (ii) as a white solid. Yield: 5.6mg

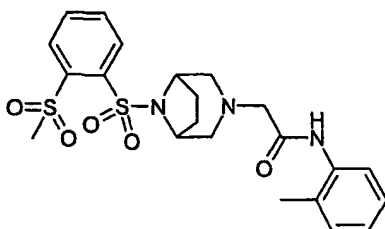
MS: ESI (+ve) 419 (M+1)

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 8.72(bs, 1H), 8.04(d, 1H), 7.21(t, 2H), 7.08(t, 1H), 4.18(m, 2H), 3.20(s, 2H), 2.88(dd, 2H), 2.66(s, 3H), 2.61(d, 2H), 2.44(s, 3H), 2.31(s, 3H), 2.03(m, 4H)

20

### Example 89

*cis*-2-[4-(2-Methanesulphonylbenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide



The title compound was prepared from the product of Example 20 step (iv) (0.34mmol) and 2-methanesulphonylbenzenesulphonyl chloride (0.34mmol) by the method of Example 58 step (ii) as a white solid. Yield: 13mg

5

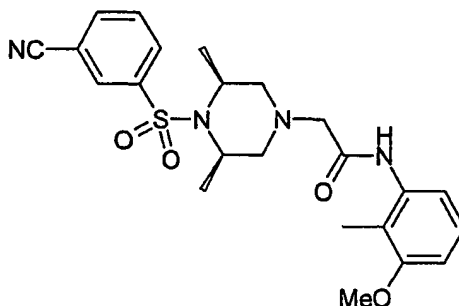
MS: ESI (+ve) 478 (M+1)

<sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>) 8.81(bs, 1H), 8.40(m, 1H), 8.28(m, 1H), 8.03(d, 1H), 7.80(m, 2H), 7.25-7.17(m, 2H), 7.06(t, 1H), 4.48(m, 2H), 3.46(s, 3H), 3.16(s, 2H), 2.82(dd, 2H), 2.68(d, 2H), 2.29(s, 3H), 1.95(d, 4H)

10

#### Example 90

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(3-methoxy-2-methylphenyl)acetamide



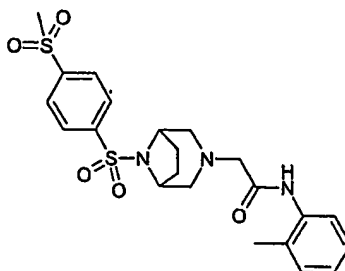
15 The title compound was prepared from the product of Example 65 step (i) (0.503mmol) and 3-cyanobenzenesulphonyl chloride (0.503mmol) by the method of Example 58 step (ii) as a white solid. Yield: 21mg

MS: ESI (+ve) 424 (M+1)

20 <sup>1</sup>H NMR  $\delta$  (CD<sub>3</sub>OD) 7.77(s, 1H), 7.67(s, 1H), 7.43(d, 1H), 7.20(q, 1H), 6.95(t, 1H), 4.12-4.20(m, 2H), 3.78(s, 3H), 3.12(s, 2H), 2.72(d, 2H), 2.17-2.23(m, 5H), 1.54(d, 6H)

**Example 91**

***cis*-2-[4-(4-Methanesulphonylbenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide**



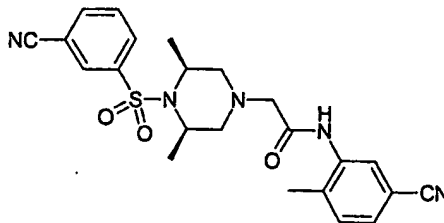
The title compound was prepared from the product of Example 20 step (iv) (0.34mmol) and 4-methanesulphonylbenzenesulphonyl chloride (0.34mmol) by the method of Example 58 step (ii) as a white solid. Yield: 25mg

MS: ESI (+ve) 478 (M+1)

<sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>) 8.69(bs, 1H), 8.10(q, 4H), 8.04(d, 1H), 7.25-7.17(m, 2H), 7.07(t, 1H), 4.28(m, 2H), 3.20(s, 2H), 3.11(s, 3H), 2.87(dd, 2H), 2.67(d, 2H), 2.27(s, 3H), 1.93(m, 2H), 1.74(m, 2H)

**Example 92**

***cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(5-cyano-2-methylphenyl)acetamide**

**i) 2-Chloro-N-(5-cyano-2-methylphenyl)acetamide**

The subtitle compound was prepared from 5-cyano-2-methylaniline (1.6g) and chloroacetyl chloride (1.1ml) by the method of Example 33 step (iii) as a white solid. Yield: 1.85g

MS: APCI (-ve) 207 (M-1)

**ii) *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(5-cyano-2-methylphenyl)acetamide**

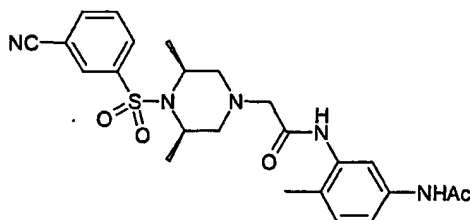
The title compound was prepared from the product of step (i) (0.19g) and the product from Example 80 step (ii) (0.2g) by the method of Example 80 step (iii) as a white solid. Yield: 0.25g

MS: APCI(+ve) 452 (M+1)

<sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>) 8.81(bs, 1H), 8.49(s, 1H), 8.13(s, 1H), 8.05(d, 1H), 7.90(d, 1H), 7.70(t, 1H), 7.29(d, 1H), 7.27(d, 1H), 4.20(m, 2H), 3.10(s, 2H), 2.70(d, 2H), 2.36(s, 3H), 2.20(m, 2H), 1.60(d, 6H)

**Example 93**

***cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(5-acetamido-2-methylphenyl)acetamide**



**i) *cis*-2-Chloro-N-(5-acetamido-2-methylphenyl)acetamide**

The subtitle compound was prepared from 5-acetamido-2-methylaniline (0.5g) and chloroacetyl chloride (0.27ml) by the method of Example 33 step (iii) as a beige solid. Yield: 0.55g

MS: APCI(+ve) 241 (M+1)

**ii) *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(5-acetamido-2-methylphenyl)acetamide**

The title compound was prepared from the product of step (i) (0.22g) and the product of Example 80 step (ii) (0.2g) by the method of Example 80 step (iii) as a white solid.

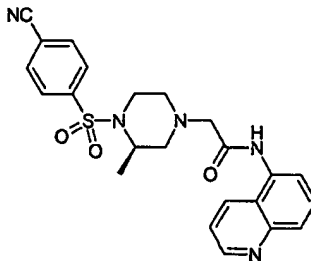
Yield: 0.11g

MS: APCI(+ve) 468 (M+1)

<sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>) 9.60(bs, 1H), 8.78(bs, 1H), 8.19(s, 1H), 8.17(d, 1H), 8.05(s, 1H),  
5 7.98(d, 1H), 8.77(t, 1H), 7.75(s, 1H), 7.50(d, 1H), 7.10(d, 1H), 4.10(m, 2H), 2.75(d, 2H),  
2.25(s, 3H), 2.16(m, 2H), 2.10(s, 3H), 1.50(d, 6H)

#### Example 94

(R)-2-[4-(4-Cyanobenzenesulphonyl)-3-methylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide  
10 yl)acetamide



##### i) (R)-2-(3-Methylpiperazin-1-yl)-N-(quinolin-5-yl)acetamide

The subtitle compound was prepared from 2-chloro-N-(quinolin-5-yl)acetamide (1g) (J  
Indian Chem Soc, 1940, 17, 619-621) and (R)-2-methylpiperazine (0.5g) by the method of  
15 Example 58 step (i) as a white solid. Yield: 1.4g

MS; APCI(+ve) 285 (M+1)

##### ii) (R)-2-[4-(4-Cyanobenzenesulphonyl)-3-methylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide 20 yl)acetamide

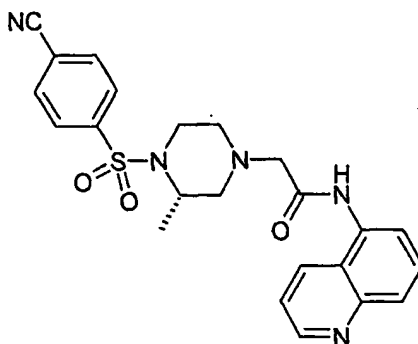
The title compound was prepared from the product of step (i) (1.4g) and 4-cyanobenzenesulphonyl chloride (1g) by the method of Example 58 step (ii) as a white solid. Yield: 0.41g

25 MS: APCI(+ve) 450 (M+1)

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 9.30(s, 1H), 8.95(d, 1H), 8.09(m, 2H), 7.99-7.94(m, 3H), 7.86-7.82(d, 2H), 7.73(m, 1H), 7.43(m, 1H), 4.27(m, 1H), 3.78(d, 1H), 3.42(m, 1H), 3.26(q, 2H), 2.98(d, 1H), 2.82(d, 1H), 2.55(dd, 1H), 2.39(m, 1H), 1.35(d, 3H)

5 **Example 95**

**(S)-2-[4-(4-Cyanobenzenesulphonyl)-3-methylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide**



**i) (S)-2-(3-Methylpiperazin-1-yl)-N-(quinolin-5-yl)acetamide**

10 The subtitle compound was prepared from 2-chloro-N-(quinolin-5-yl)acetamide (1g) (J Indian Chem Soc, 1940, 17, 619-621) and (S)-2-methylpiperazine (0.5g) by the method of Example 58 step (i) as a white solid. Yield: 1.4g

MS: APCI(+ve) 285 (M+1)

15 **ii) (S)-2-[4-(4-Cyanobenzenesulphonyl)-3-methylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide**

The title compound was prepared from the product of step (i) (1.4g) and 4-cyanobenzenesulphonyl chloride (1g) by the method of Example 58 step (ii) as a white solid. Yield: 0.53g

20

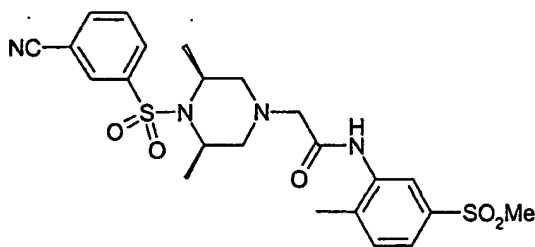
MS: APCI(+ve) 450 (M+1)

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 9.30(s, 1H), 8.95(d, 1H), 8.09(m, 2H), 7.99-7.94(m, 3H), 7.86-7.82(d, 2H), 7.73(m, 1H), 7.43(m, 1H), 4.27(m, 1H), 3.78(d, 1H), 3.42(m, 1H), 3.26(q, 2H), 2.98(d, 1H), 2.82(d, 1H), 2.55(dd, 1H), 2.39(m, 1H), 1.35(d, 3H)



**Example 96**

**cis-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-methanesulphonylphenyl)acetamide**



**i) 2-Chloro-N-(2-methyl-5-methanesulphonylphenyl)acetamide**

The subtitle compound was prepared from 5-methanesulphonyl-2-methylaniline (0.82g) and chloroacetyl chloride (0.72ml) by the method of Example 33 step (iii) as a beige solid. Yield: 0.61g

MS: APCI -ve) 260 (M-1)

**ii) cis-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-methanesulphonylphenyl)acetamide**

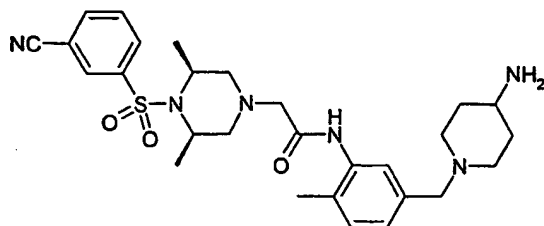
The title compound was prepared from the product of step (i) (0.14g) and the product of Example 80 step (ii) by the method of Example 80 step (iii) as a white solid. Yield: 0.03g

MS: APCI(+ve) 505 (M+1)

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 8.84(bs, 1H), 8.63(s, 1H), 8.10(s, 1H), 8.06(d, 1H), 7.90(d, 1H), 7.65(d, 1H), 7.64(d, 1H), 7.40(d, 1H), 4.25(m, 2H), 3.14(s, 2H), 3.07(s, 3H), 2.74(d, 2H), 2.40(s, 3H), 2.20(m, 2H), 1.60(d, 6H)

**Example 97**

**cis-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-(4-amino-1-piperidinyl)methyl)phenyl]acetamide**



**i) 2-Methyl-5-((1,1-dimethyl)-1-dimethylethyl)silyloxymethyl-aniline**

A mixture of 2-methyl-5-hydroxymethylaniline (10g), *tert*-butyldimethylsilyl chloride (10.84g), imidazole (12.24g) in dry N,N-dimethylformamide (80ml) were stirred at ambient temperature for 18h. The mixture was partitioned between ethyl acetate and saturated brine. The organic phase washed with water, collected, dried (MgSO<sub>4</sub>) and solvent evaporated under reduced pressure to leave a brown gum which slowly crystallised on standing. Yield: 19.2g

MS:APCI(+ve) 252 (M+1)

**ii) 2-Chloro-N-(2-methyl-5-((1,1-dimethyl)-1-dimethylethyl)silyloxymethyl)acetamide**

The subtitle compound was prepared from the product of step (i) (18.3g) and chloroacetyl chloride (17.5ml) by the method of Example 33 step (iii) as a beige solid. Yield: 23g

MS: APCI(-ve) 326(M-1)

**iii) *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-((1,1-dimethyl)-1-dimethylethyl)silyloxymethyl)phenyl]acetamide**

The subtitle compound was prepared from the product of step (ii) (1.25g) and the product of Example 80 step (ii) (1g) by the method of Example 80 step (iii) as a beige foam.

Yield: 1.3g

MS: APCI(+ve) 571 (M+1)

**iv) *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-hydroxymethyl)phenyl]acetamide**

A solution of the product of step (iii) (1.3g) in tetrahydrofuran (9ml) was treated with 1M tetrabutylammonium fluoride in tetrahydrofuran (2.6ml) at ambient temperature. After stirring for 1.5h the solvent was evaporated under reduced pressure to leave a brown gum. Purification was by silica gel chromatography eluting with ethyl acetate/ iso-hexane (9:1) to give the subtitle compound as a white solid. Yield: 0.93g

MS: APCI(+ve) 457 (M+1)

**v) *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-iodomethyl)phenyl]acetamide**

The product from step (iv) (0.1g) in tetrahydrofuran (2ml), N,N-diisopropylethylamine (0.15ml), potassium iodide (2mg) was treated with methanesulphonyl chloride (0.34ml).

After stirring at ambient temperature for 40h. The solvent was evaporated under reduced pressure to leave a beige gum. This was used directly in the next step.

**vi) *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-(4-amino-1-piperidinyl)methyl)phenyl]acetamide**

The crude product from step (v) (0.2g) was treated with 1,1-dimethylethyl, 4-aminopiperidinyl-4-carboxylate (0.13g) in tetrahydrofuran (2ml) at 55 °C for 24h. The solvent was evaporated under reduced pressure. The residue was then treated with 4M hydrogen chloride in 1,4-dioxane (3ml) for 5h. The solvents were then evaporated under reduced pressure. Purification was by reverse phase HPLC to give the title compound as a white solid. Yield. 0.1g

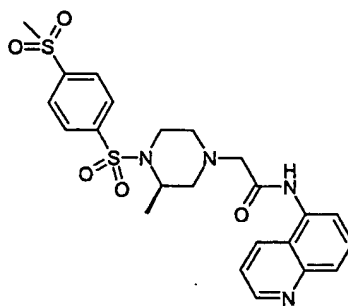
MS: APCI(+ve) 539 (M+1)

<sup>1</sup>H NMR δ (DMSO) 9.84(bs, 1H), 9.19(s, 1H), 8.33(s, 1H), 8.16(m, 4H), 7.82(t, 1H), 7.76(s, 1H), 7.32(d, 1H), 7.19(d, 1H), 4.22(s, 2H), 4.11(m, 2H), 3.41(d, 2H), 3.25(bs, 2H),

3.10(s, 2H), 3.01(m, 2H), 2.70(d, 2H), 2.40(m, 2H), 2.34(s, 3H), 2.08(d, 2H), 1.96(dd, 2H), 1.75(q, 2H), 1.45(d, 6H)

### Example 98

- 5    **(R)-2-[4-(4-Methanesulphonylbenzenesulphonyl)-3-methylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide**



- i) **(R)-1,1-Dimethylethyl, (4-Methanesulphonylbenzenesulphonyl)-3-methylpiperazin-1-yl-1-carboxylate**

- 10    The subtitle compound was prepared from (R)-1,1-dimethylethyl, 3-methylpiperazin-1-yl-1-carboxylate (0.75g) (J. Med. Chem, 1993, 36(6), 690) and 4-methanesulphonylbenzenesulphonyl chloride (0.96g) by the method of Example 58 step (ii) as white solid.  
Yield: 0.9g

- 15    <sup>1</sup>H NMR δ (DMSO) 8.15(d, 2H), 8.07(d, 2H), 4.08(bs, 1H), 3.85(bs, 1H), 3.65(bs, 1H), 3.33(s, 2H), 3.32(s, 3H), 3.09(t, 1H), 1.36(s, 9H), 0.93(d, 3H)

- ii) **(R)-1-(4-Methanesulphonylbenzenesulphonyl)-3-methylpiperazine, hydrochloride salt**

- 20    The subtitle compound was prepared from the product of step (i) (0.209g) by the method of Example 27 step (iv) as a white solid. Yield: 0.15g

MS:APCI(+ve) 319(M+1)

**iii) (R)-2-[4-(4-Methanesulphonylbenzenesulphonyl)-3-methylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide**

The title compound was prepared from the product of step (ii) (0.14g) and 2-chloro-N-(quinolin-5-yl)acetamide (0.97g) (J Indian Chem Soc, 1940, 17, 619-621) by the method of

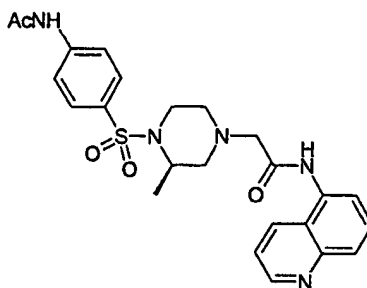
5 Example 33 step (iv) as a white solid. Yield: 0.135g

MS: APCI(+ve) 503(M+1)

<sup>1</sup>H NMR  $\delta$  (DMSO) 9.88(s, 1H), 8.91(d, 1H), 8.32(d, 1H), 8.16(d, 2H), 8.09(d, 2H),  
7.88(dd, 1H), 7.73(m, 2H), 7.55(q, 1H), 4.09(d, 1H), 3.66(d, 1H), 3.38(d, 1H), 3.31(s, 3H),  
10 3.22(s, 2H), 2.91(d, 1H), 2.73(d, 1H), 2.31(m, 2H), 2.15(t, 1H), 1.21(d, 3H)

**Example 99**

**(R)-2-[4-(4-Acetamidobenzenesulphonyl)-3-methylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide**



15

**i) (R)-1,1-Dimethylethyl, (4-Acetamidobenzenesulphonyl)-3-methylpiperazin-1-yl-1-carboxylate**

The subtitle compound was prepared from (R)-1,1-dimethylethyl, 3-methylpiperazin-1-yl-1-carboxylate (4g) (J. Med. Chem, 1993, 36(6), 690) and 4-acetamidobenzenesulphonyl  
20 chloride (4.68g) by the method of Example 58 step (ii) as white solid. Yield: 4.9g

MS: APCI(+ve) 398(M+1)

25 **ii) (R)-1-(4-Acetamidobenzenesulphonyl)-3-methylpiperazine, hydrochloride salt**

The subtitle compound was prepared from the product of step (i) (4.9g) by the method of Example 27 step (iv) as a white solid. Yield: 4.38g

<sup>1</sup>H NMR δ (DMSO) 10.60(s, 1H), 8.92(bs, 1H), 8.91(d, 2H), 8.04(t, 1H), 7.85(d, 2H),  
 5 7.78(d, 2H), 7.45(d, 1H), 6.66(d, 1H), 3.27(t, 2H), 3.06(m, 2H), 2.87(m, 2H), 2.73(m, 3H),  
 2.10(s, 3H), 1.30(d, 2H), 1.16(d, 3H)

**iii) (R)-2-[4-(4-Acetylamino benzenesulphonyl)-3-methylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide**

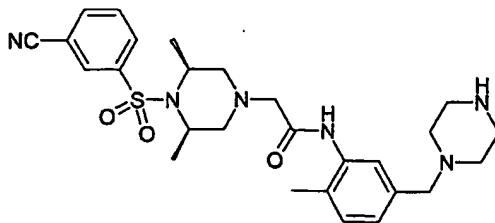
10 The title compound was prepared from the product of step (ii) (0.65g) and 2-chloro-N-(quinolin-5-yl)acetamide (0.39g) (J Indian Chem Soc, 1940, 17, 619-621) by the method of Example 33 step (iv) as a white solid. Yield: 0.064g

MS: APCI(+ve) 439(M-42(+H,-Ac))

15 <sup>1</sup>H NMR δ (DMSO) 9.89(s, 1H), 8.91(s, 1H), 8.31(d, 1H), 7.87(m, 1H), 7.75(s, 2H),  
 7.50(m, 1H), 7.43(d, 2H), 6.63(d, 2H), 6.01(s, 2H), 3.90(s, 1H), 3.42(d, 1H), 3.42(d, 1H),  
 3.24(s, 1H), 3.20(d, 2H), 2.86(d, 1H), 2.68(d, 1H), 2.31(d, 1H), 2.18(t, 1H), 1.18(d, 3H)

**Example 100**

20 **cis-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-(1-piperazinylmethyl)phenyl)acetamide**



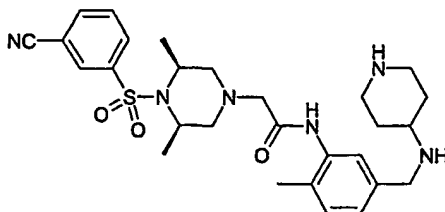
The title compound was prepared from the product of Example 97 step (v) (0.2g) and 1,1-dimethylethyl, piperazine-1-carboxylate (0.12g) by the method of Example 97 step (vi) to  
 25 give the title compound as a white solid. Yield: 74mg

MS: APCI(+ve) 525 (M+1)

<sup>1</sup>H NMR δ (DMSO) 9.21(s, 1H), 9.0(bs, 2H), 8.33(s, 1H), 8.17(d, 2H), 7.82(t, 1H), 7.69(s, 1H), 7.28(d, 1H), 7.16(d, 1H), 4.14(m, 2H), 3.27(bs, 4H), 3.15(s, 2H), 3.05(bs, 2H), 2.69(d, 2H), 2.21(s, 3H), 2.0(d, 2H), 1.44(d, 6H)

5 **Example 101**

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-(4-piperidinylamino)methyl)phenyl)acetamide



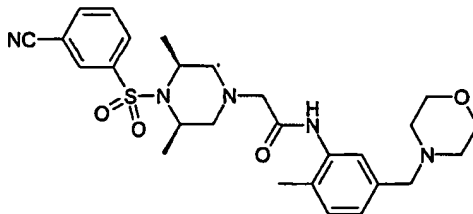
10 The title compound was prepared from the product of Example 97 step (v) (0.2g) and 1,1-dimethylethyl, 4-aminopiperidinyl-1-carboxylate (0.12g) by the method of Example 97 step (vi) as a white solid. Yield: 34mg

MS: APCI(+ve) 539(M+1)

15 <sup>1</sup>H NMR δ (DMSO) 9.18(s, 1H), 9.09(s, 2H), 8.81(m, 1H), 8.60(m, 1H), 8.33(s, 1H), 8.15(d, 2H), 7.82(t, 1H), 7.75(s, 1H), 7.30(d, 1H), 7.21(d, 1H), 4.10(m, 4H), 3.40(d, 2H), 3.32(s, 2H), 2.92(q, 2H), 2.68(d, 2H), 2.23(s, 3H), 1.94(dd, 2H), 1.73(q, 2H), 1.43(d, 6H)

**Example 102**

20 *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-(1-morpholinyl)methyl)phenyl)acetamide



The title compound was prepared from the product of Example 97 step (v) (0.2g) and morpholine (0.058g) by the method of Example 97 step (vi). The solvents evaporated

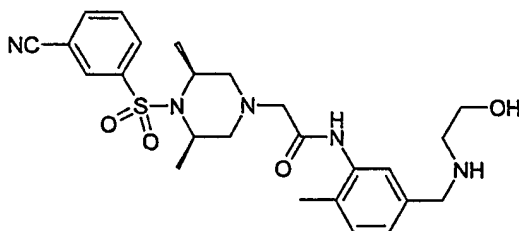
under reduced pressure and the residue purified by reverse phase HPLC to give the title compound as a white solid. Yield: 97mg

MS: APCI(+ve) 526 (M+1)

5  $^1\text{H}$  NMR  $\delta$  (DMSO) 10.11(bs, 1H), 9.22(s, 1H), 8.34(s, 1H), 8.16(d, 2H), 7.83(d, 1H), 7.78(d, 1H), 7.33(d, 1H), 7.21(d, 1H), 4.31(s, 2H), 4.12(t, 4H), 3.63(m, 2H), 3.3(m, 4H), 2.70(d, 2H), 2.23(s, 3H), 1.97(dd, 2H), 1.43(d, 6H)

#### Example 103

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-(2-  
10 hydroxyethylamino)methyl)phenyl)acetamide



The title compound was prepared from the product of Example 97 step (v) (0.2g) and ethanolamine (0.041 g) by the method of Example 97 step (vi). The solvents evaporated  
15 under reduced pressure and the residue purified by reverse phase HPLC to give the title compound as a white solid. Yield: 37mg

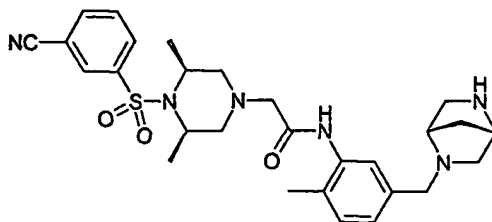
MS: APCI(+ve) 500(M+1)

$^1\text{H}$  NMR  $\delta$  (DMSO) 8.27(s, 1H), 8.18(d, 1H), 8.02(d, 1H), 7.74-7.82(m, 3H), 7.35(d, 2H),  
20 7.25(d, 1H), 4.27(t, 2H), 4.20(s, 2H), 3.83(t, 2H), 3.40(s, 2H), 3.25(s, 1H), 3.14(t, 2H), 2.97(d, 2H), 2.33(s, 5H), 1.56(d, 6H)

#### Example 104

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-(S,S)-  
25 (2,5-diazabicyclo[2.2.1]hept-2-yl)methyl)phenyl)acetamide





The title compound was prepared from the product of Example 97 step (v) (0.2g) and 1,1-dimethylethyl, (S,S)-2,5-diazabicyclo[2.2.1]heptane-5-carboxylate (0.13g) by the method of Example 97 step (vi) as a white solid. Yield: 107mg

5

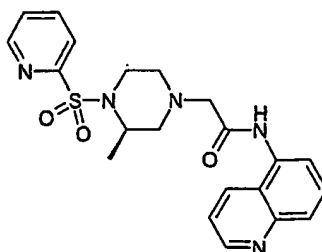
MS: APCI(+ve) 537 (M+1)

<sup>1</sup>H NMR  $\delta$  (DMSO) 9.2(s, 1H), 8.34(s, 1H), 8.16(d, 2H), 7.83(d, 1H), 7.79(s, 1H), 7.31(d, 1H), 7.24(d, 1H), 4.46(s, 1H), 4.32(m, 2H), 4.12(s, 2H), 3.35(d, 2H), 3.11(s, 2H), 2.68(d, 2H), 2.23(s, 3H), 1.98(t, 3H), 1.44(d, 6H)

10

### Example 105

**(R)-2-[4-(2-Pyridinesulphonyl)-3-methylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide**



**i) (R)-1,1-Dimethylethyl, (2-Pyridinesulphonyl)-3-methylpiperazin-1-yl-1-carboxylate**

15 A solution of 1,1-dimethylethyl, 3-(R)-methylpiperazine-1-carboxylate (2g) (J. Med. Chem, 1993, 36(6), 690), 4-N,N'-dimethylaminopyridine (1.22g) in pyridine (10ml) was treated with 2-pyridinesulphonyl chloride (2.7g) at 0 °C. The ice bath was removed and the mixture further stirred for 1h at ambient temperature. The mixture was partitioned between dichloromethane and water. The organic phase further washed with brine, collected, dried  
20 (MgSO<sub>4</sub>) and solvent evaporated under reduced pressure. Purification was by silica gel chromatography eluting with ethyl acetate/dichloromethane mixtures to give the subtitle compound as white solid. Yield: 3.3g

MS: ESI(+ve) 342(M+1)

**ii) (R)-1-(2-Pyridinesulphonyl)-3-methylpiperazine, hydrochloride salt**

The subtitle compound was prepared from the product of step (i) (2.5g) by the method of

5 Example 27 step (iv) as a white solid. Yield: 2.5g

MS: ESI(+ve) 242 (M+1)

**iii) (R)-2-[4-(2-Pyridinesulphonyl)-3-methylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide**

10

The title compound was prepared from the product of step (ii) (0.6g) and 2-chloro-N-(quinolin-5-yl)acetamide (0.39g) (J Indian Chem Soc, 1940, 17, 619-621) by the method of Example 80 step (iii). Purification was by silica gel chromatography eluting with ethyl acetate to give a white solid. Yield: 0.41g

15

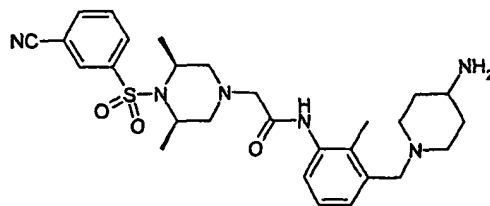
MS: ESI(+ve) 424(M+1)

<sup>1</sup>H NMR δ (DMSO) 8.8(d, 1H), 8.35(d, 1H), 8.10(t, 1H), 7.97(d, 1H), 7.90(d, 1H), 7.7(m, 3H), 7.55(m, 1H), 4.10(m, 1H), 3.7(m, 1H) 3.5(t, 1H), 3.3(m, 2H), 3.2(m, 1H), 2.95(d, 1H), 2.7(d, 1H), 2.4-2.1(m, 2H), 1.2(d, 3H)

20

**Example 106**

**cis-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-3-(4-amino-1-piperidinyl)methyl)phenyl]acetamide**



25

**i) 2-Methyl-3-((1,1-dimethyl)-1-dimethylethyl)silyloxymethylaniline**

The subtitle compound was prepared from 2-methyl-3-hydroxymethylaniline (5g) and *tert*-butyldimethylsilyl chloride (5.42g) by the method of Example 97 step (i) as an oil which crystallised on standing. Yield: 9.12g

5 MS: APCI(+ve) 252(M+1)

**ii) 2-Chloro-N-(2-methyl-3-((1,1-dimethyl)-1-dimethylethyl)silyloxymethyl)acetamide**

The subtitle compound was prepared from the product of step (i) (4.13g) and chloroacetyl chloride (1.5ml) by the method of Example 33 step (iii) as a beige solid. Yield: 3.12g

10

MS:APCI(+ve) 328(M+1)

**iii) *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-((1,1-dimethyl)-1-dimethylethyl)silyloxymethyl)phenyl]acetamide**

15 The subtitle compound was prepared from the product of step (ii) (1.25g) and the product of Example 80 step (ii) (1g) by the method of Example 80 step (iii) as a cream solid.

Yield: 1.5g

MS: APCI(+ve) 571(M+1)

20

**iv) *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-hydroxymethyl)phenyl]acetamide**

The subtitle compound was prepared from the product of step (iii) (1.4g) and 1M tetrabutylammonium fluoride in tetrahydrofuran (2.7ml) by the method of Example 97 step

25 (iv) as a white solid. Yield: 1g

MS:APCI(+ve) 457(M+1)

**v) *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-3-iodomethyl)phenyl]acetamide**

30

The product from step (iv) (0.1g) in tetrahydrofuran (2ml), N,N-diisopropylethylamine (0.15ml), potassium iodide (2mg) was treated with methanesulphonyl chloride (0.34ml). After stirring at ambient temperature for 40h. The solvent was evaporated under reduced pressure to leave a beige gum. This was used directly in the next step.

5

vi) **cis-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-(4-amino-1-piperidinyl)methyl)phenyl]acetamide**

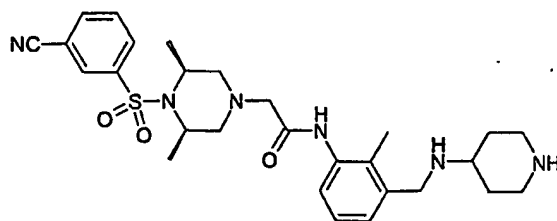
The crude product from step (v) (0.2g) was treated with 1,1-dimethylethyl, 4-aminopiperidinyl-4-carboxylate (0.13g) in tetrahydrofuran (2ml) at 55 °C for 24h. The solvent was evaporated under reduced pressure. . The residue was then treated with 4M hydrogen chloride in 1,4-dioxane (3ml) for 5h. The solvents were then evaporated under reduced pressure. Purification was by reverse phase HPLC to give the title compound as a white solid. Yield. 0.068g

15 MS: APCI(+ve) 539 (M+1)

<sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>/DMSO) 8.87(bs, 1H), 8.67(bs, 1H), 8.14(s, 1H), 8.10(d, 1H), 7.95(d, 1H), 7.80(d, 1H), 7.75(t, 1H), 7.30(m, 2H), 4.30(bs, 1H), 4.20(m, 2H), 3.10(s, 2H), 2.80(d, 2H), 2.30(s, 3H), 2.20(m, 4H), 1.60(d, 6H)

20 **Example 107**

**cis-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-3-(4-piperidinylamino)methyl)phenyl]acetamide**

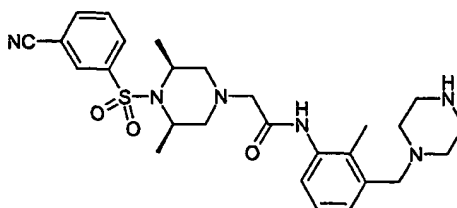


MS: APCI(+ve) 539(M+1)

<sup>1</sup>H NMR  $\delta$  (DMSO) 9.33(bs, 1H), 9.10(bs, 1H), 8.8(bd, 1H), 8.60(bd, 1H), 8.37(s, 1H),  
8.20(m, 1H), 7.90(t, 1H), 7.40(d, 1H), 7.30(m, 2H), 4.20(bs, 2H), 4.10(m, 2H), 3.10(s, 2H),  
3.00(m, 2H), 2.7(m, 2H), 2.30(m, 2H), 2.20(s, 3H), 2.00-1.80(m, 4H), 1.40(s, 6H)

### Example 108

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-3-(1-piperazinylmethyl)phenyl)acetamide



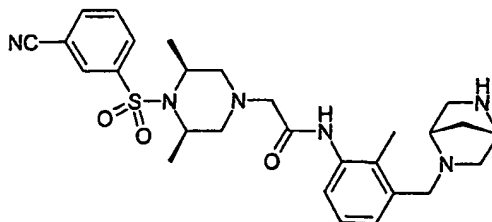
The title compound was prepared from the product of Example 106 step (v) (0.2g) and 1,1-dimethylethyl, piperazine-1-carboxylate (0.12g) by the method of Example 106 step (vi) as a white solid. Yield: 74mg

MS: APCI(+ve) 525 (M+1)

<sup>1</sup>H NMR  $\delta$  (DMSO) 8.34(s, 1H), 8.20(m, 2H), 7.80(t, 1H), 7.40(t, 1H), 7.20(2xd, 2H),  
4.20(m, 2H), 3.90(bs, 2H), 3.20(m, 6H), 3.00-2.60(m, 6H), 2.20(s, 3H), 2.00(m, 2H),  
1.50(d, 6H)

### Example 109

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-3-(S,S)-(2,5-diazabicyclo[2.2.1]hept-2-yl)methyl)phenyl)acetamide



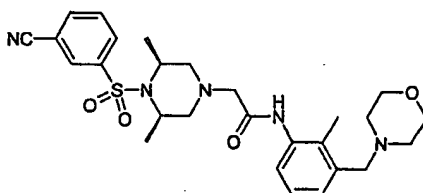
The title compound was prepared from the product of Example 106 step (v) (0.2g) and 1,1-dimethylethyl, (S,S)-2,5-diazabicyclo[2.2.1]heptane-5-carboxylate (0.13g) by the method of Example 106 step (vi) as a white solid. Yield: 82mg

5 MS: APCI(+ve) 537 (M+1)

<sup>1</sup>H NMR δ (DMSO) 8.38(s, 1H), 8.20(m, 2H), 7.80(t, 1H), 7.50(d, 1H), 7.30(m, 2H), 4.40(s, 1H), 4.30(m, 2H), 4.10(m, 2H), 3.30(m, 2H), 3.10(s, 2H), 2.80(m, 2H), 2.22(s, 3H), 2.00(m, 4H), 1.50(d, 6H)

#### 10 Example 110

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-3-(1-morpholinyl)methyl)phenyl)acetamide



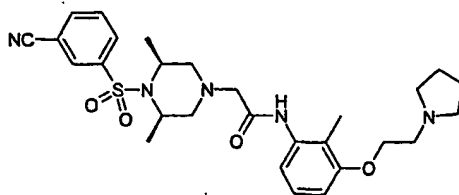
The title compound was prepared from the product of Example 106 step (v) (0.2g) and morpholine (0.058g) by the method of Example 106 step (vi) as a white solid. Yield: 69mg

MS: APCI(+ve) 526 (M+1)

<sup>1</sup>H NMR δ (DMSO) 8.34(s, 1H), 8.20(m, 2H), 7.80(t, 1H), 7.60(d, 1H), 7.40(m, 2H), 4.40(s, 2H), 4.20(m, 2H), 4.00(bs, 2H), 3.70(bs, 2H), 3.30(bs+s, 6H), 2.80(d, 2H), 2.30(s, 3H), 2.00(m, 2H), 1.50(d, 6H)

#### Example 111

*Cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-3-(2-(1-pyrrolidinyl)ethoxy)phenyl)acetamide



**i) 2-Methyl-3-((1,1-dimethyl)-1-dimethylethyl)silyloxyaniline**

The subtitle compound was prepared from 3-amino-2-methylphenol (10g) and *tert*-butyldimethylsilyl chloride(12.22g) by the method of Example 97 step (i) as a brown oil.

Yield: 15g

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 6.86(t, 1H), 6.33(d, 1H), 6.27(d, 1H), 3.58(bs, 2H), 2.04(s, 3H), 1.01(s, 9H), 0.20(s, 6H)

**ii) 2-Chloro-N-(2-methyl-3-((1,1-dimethyl)-1-dimethylethyl)silyloxy)phenyl)acetamide**

The product from step (i) (5g), PyBrop (9.82g), chloroacetic acid (1.99g), N,N-diisopropylethylamine (11ml) in dichloromethane (100ml) were stirred at ambient temperature for 16h. The mixture was partitioned between water and dichloromethane, the organic phase collected, dried (MgSO<sub>4</sub>) and solvent evaporated under reduced pressure.

Purification was by silica gel chromatography eluting with 10% diethyl ether in iso-hexane containing 1% triethylamine to give the subtitle compound as a pale yellow oil. Yield: 3.5g

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 8.21(bs, 1H), 7.48(d, 1H), 7.09(t, 1H), 6.68(d, 1H), 4.23(s, 2H), 2.16(s, 3H), 1.02(s, 9H), 0.22(s, 6H)

**iii) Cis-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-3-((1,1-dimethyl)-1-dimethylethyl)silyloxy)phenyl)acetamide**

The subtitle compound was prepared from the product of step (ii) (1g) and the product of Example 80 step (ii) (0.89g) by the method of Example 80 step (iii) as a beige solid. Yield:

1.6g

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 8.67(s, 1H), 8.12(s, 1H), 8.03(d, 1H), 7.85(d, 1H), 7.67(t, 1H), 7.59(d, 1H), 7.07(t, 1H), 6.64(d, 1H), 4.05-4.10(m, 2H), 3.10(s, 2H), 2.73(d, 2H), 2.19(d, 2H), 2.10(s, 3H), 1.54(s, 6H), 1.01(s, 9H), 0.22(s, 6H)

5    **iv) *Cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-3-hydroxy)phenyl)acetamide**

The subtitle compound was prepared from the product of step (iii) (1.6g) and tetra-butylammonium fluoride (3.18ml) by the method of Example 97 step (iv) as a white solid  
Yield: 0.5g

10    MS APCI(+ve) 443 (M+1)

**v) *Cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-3-(2-(1-pyrrolidinyl)ethoxy)phenyl)acetamide**

15    The product from step (iv) (0.1g), 1-(2-chloroethyl)pyrrolidine hydrochloride (76mg), cesium carbonate (0.36g) in 1-methyl-2-pyrrolidinone (2ml) were stirred at 70 °C for 16h. The mixture was partitioned between ethyl acetate and water, the organic phase collected, dried (MgSO<sub>4</sub>) and solvent evaporated under reduced pressure. Purification was by reverse phase HPLC eluting with 5 to 90% methanol in 0.1% aqueous trifluoroacetic acid  
20    to give the the title compound as a white solid. Yield: 7mg

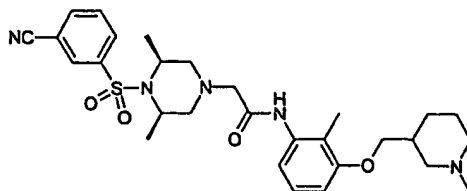
MS: APCI(+ve) 540(M+1)

<sup>1</sup>H NMR δ (CD<sub>3</sub>OD) 8.15(s, 1H), 8.05(d, 1H), 7.89(d, 1H), 7.67(t, 1H), 7.06(s, 1H), 7.04(s, 1H), 6.74(t, 1H), 4.01-4.09(m, 4H), 2.99(s, 2H), 2.88(t, 2H), 2.61-2.66(m, 6H), 2.05(s, 25    3H), 1.95(dd, 2H), 1.71-1.77(m, 4H), 1.44(d, 6H)

**Example 112**

**(±) *Cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-3-(1-methylpiperidin-3-yl)methoxy)phenyl)acetamide**





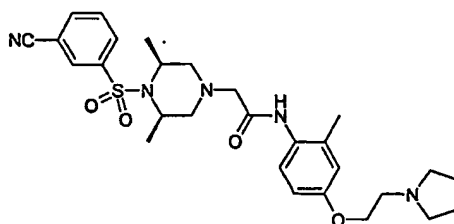
The title compound was prepared from the product of Example 111 step (iv) (0.1g) and (±) 1-methyl-3-chloromethylpiperidine (83mg) by the method of Example 111 step (v) as a white solid. Yield: 19mg

MS: APCI(+ve) 554 (M+1)

<sup>1</sup>H NMR δ (CD<sub>3</sub>OD) 8.24(s, 1H), 8.14(d, 1H), 7.98(d, 1H), 7.77(t, 1H), 7.10-7.15(m, 2H), 6.78-6.81(m, 1H), 4.12-4.18(m, 2H), 3.80-3.92(m, 2H), 3.09(s, 3H), 2.75-2.85(m, 1H), 2.74(d, 2H), 2.31(s, 3H), 2.12(s, 3H), 1.64-2.17(m, 8H), 1.53(d, 6H), 1.15-1.19(m, 2H)

### Example 113

***Cis-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-4-(2-(1-pyrrolidinyl)ethoxy)phenyl)acetamide***



#### i) 2-Methyl-4-((1,1-dimethyl)-1-dimethylethyl)silyloxyaniline

The subtitle compound was prepared from 4-amino-3-methylphenol (10g) and *tert*-butyldimethylsilyl chloride(12.22g) by the method of Example 97 step (i) as a brown oil. Yield: 14g

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 6.53-6.58(m, 3H), 3.33(bs, 2H), 2.12(s, 3H), 0.98(s, 9H), 0.15(s, 6H)

#### ii) 2-Chloro-N-(2-methyl-3-((1,1-dimethyl)-1-dimethylethyl)silyloxy)phenyl)acetamide

The subtitle compound was prepared from the product of step (i) (5g) by the method of Example 111 step (ii) as pale yellow oil. Yield: 5g

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 8.06(bs, 1H), 7.57-7.60(m, 1H), 6.53-6.58(m, 3H), 3.33(bs, 2H),  
2.12(s, 3H), 0.98(s, 9H), 0.15(s, 6H)

iii) *Cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-4-((1,1-dimethyl)-1-dimethylethyl)silyloxy)phenyl)phenyl)acetamide

The subtitle compound was prepared from the product of step (ii) (1g) and the product of Example 80 step (ii) (0.89g) by the method of Example 80 step (iii) as a white solid. Yield: 1.6g

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 8.48(s, 1H), 8.12(s, 1H), 8.04(d, 1H), 7.86(d, 1H), 7.64-7.70(m, 2H), 6.67-6.70(m, 2H), 4.11-4.15(m, 2H), 3.08(s, 2H), 2.73(d, 2H), 2.22(s, 3H), 2.16(dd, 2H),  
1.55(d, 6H), 0.97(s, 9H), 0.18(s, 6H)

iv) *Cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-4-hydroxy)phenyl)acetamide

The subtitle compound was prepared from the product of step (iii) (1.6g) and tetrabutylammonium fluoride (3.21ml) by the method of Example 97 step (iv) as a white solid Yield: 0.4g

MS APCI(+ve) 443 (M+1)

v) *Cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-4-(2-(1-pyrrolidinyl)ethoxy)phenyl)acetamide

The title compound was prepared from the product of step (iv) (0.1g) and 1-(2-chloroethyl)pyrrolidine hydrochloride (76mg) by the method of Example 111 step (v) as a white solid. Yield: 10mg

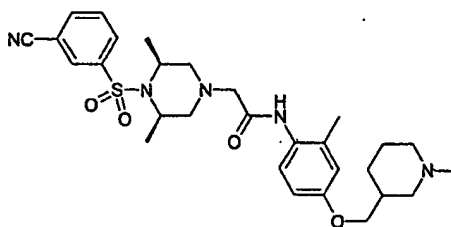
MS: APCI(+ve) 540 (M+1)

<sup>1</sup>H NMR δ (CD<sub>3</sub>OD) 8.24(s, 1H), 8.15(d, 1H), 7.98(d, 1H), 7.77(t, 1H), 7.30(d, 1H), 6.83(d, 1H), 6.77(dd, 1H), 4.13-4.18(m, 2H), 4.10(t, 2H), 3.07(s, 2H), 2.91(t, 2H), 2.73(d, 2H), 2.65-2.69(m, 4H), 2.25(s, 3H), 2.04(dd, 2H), 1.79-1.86(m, 4H), 1.53-1.54(d, 6H),

5

#### Example 114

(±) *Cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-4-(1-methylpiperidin-3-yl)methoxy)phenyl)acetamide



10

The title compound was prepared from the product of Example 113 step (iv) (0.1g) and (±) 1-methyl-3-chloromethylpiperidine (83mg) by the method of Example 111 step (v) as a white solid. Yield: 19mg

15

MS: APCI(+ve) 554 (M+1)

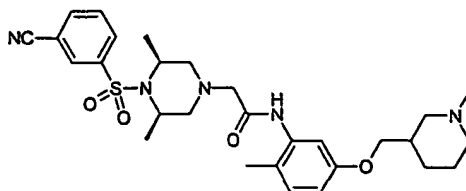
<sup>1</sup>H NMR δ (CD<sub>3</sub>OD) 8.24(s, 1H), 8.15(d, 1H), 7.98(d, 1H), 7.77(t, 1H), 7.29(d, 1H), 6.79(d, 1H), 6.74(dd, 1H), 4.13-4.16(m, 2H), 3.75-3.88(m, 2H), 3.08(s, 2H), 3.02-3.04(m, 1H), 2.82-2.85(m, 1H), 2.73(d, 2H), 2.29(s, 3H), 2.21(s, 3H), 1.62-2.10(m, 8H), 1.53(d, 6H), 1.09-1.13(m, 1H),

20

#### Example 115

(±) *Cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-5-(1-methylpiperidin-3-yl)methoxy)phenyl)acetamide

25



**i) 2-Methyl-5-((1,1-dimethyl)-1-dimethylethyl)silyloxyaniline**

The subtitle compound was prepared from 3-amino-4-methylphenol (10g) and *tert*-butyldimethylsilyl chloride(12.22g) by the method of Example 97 step (i) as a brown oil.

5 Yield: 15g

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 6.84-6.88(m, 1H), 6.18-6.22(m, 2H), 3.52(bs, 2H), 2.08(s, 3H), 0.97(s, 9H), 0.17(s, 6H)

**10 ii) 2-Chloro-N-(2-methyl-5-((1,1-dimethyl)-1-dimethylethyl)silyloxy)phenyl)acetamide**

The subtitle compound was prepared from the product of step (i) (5g) by the method of Example 111 step (ii) as pale yellow oil. Yield: 5.3g

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 8.19(bs, 1H), 7.57(d, 1H), 7.03(d, 1H), 6.61(dd, 1H), 4.22(s, 2H),  
15 2.23(s, 3H), 0.98(s, 9H), 0.21(s, 6H)

**iii) *Cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-5-((1,1-dimethyl)-1-dimethylethyl)silyloxy)phenyl)phenyl)acetamide**

The subtitle compound was prepared from the product of step (ii) (1g) and the product of  
20 Example 80 step (ii) (0.89g) by the method of Example 80 step (iii) as a white solid. Yield: 1.8g

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 8.64(s, 1H), 8.12(s, 1H), 8.04(d, 1H), 7.87(d, 1H), 7.68-7.70(m, 2H),  
7.01(d, 1H), 6.56(dd, 1H), 4.09-4.16(m, 2H), 3.08(s, 2H), 2.72(d, 2H), 2.22(s, 3H),  
25 2.16(dd, 2H), 1.55(d, 6H), 0.97(s, 9H), 0.19(s, 6H)

**iv) *Cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-5-hydroxy)phenyl)acetamide**

The subtitle compound was prepared from the product of step (iii) (1.81g) and tetra-butylammonium fluoride (3.24ml) by the method of Example 97 step (iv) as a white solid

5 Yield: 0.8g

MS APCI(+ve) 443 (M+1)

**v) ( $\pm$ ) *Cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-5-(1-methylpiperidin-3-yl)methoxy)phenyl)acetamide**

The title compound was prepared from the product of step (iv) (0.1g) and ( $\pm$ ) 1-methyl-3-chloromethylpiperidine (76mg) by the method of Example 111 step (v) as a white solid.

Yield: 5mg

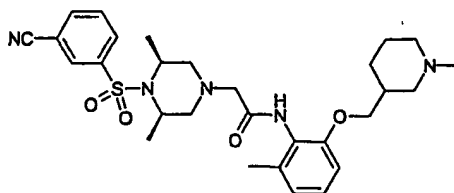
15 MS: APCI(+ve) 540 (M+1)

$^1\text{H}$  NMR  $\delta$  ( $\text{CD}_3\text{OD}$ ) 8.24(s, 1H), 8.14(d, 1H), 7.98(d, 1H), 7.77(t, 1H), 7.32(d, 1H), 7.10(d, 1H), 6.67(dd, 1H), 4.12-4.18(m, 2H), 3.73-3.86(m, 2H), 3.09(s, 2H), 3.02-3.05(m, 1H), 2.83-2.86(m, 1H), 2.74(d, 2H), 2.29(s, 3H), 2.24(s, 3H), 1.58-2.11(m, 9H), 1.54(d, 6H), 1.09-1.13(m, 1H),

20

**Example 116**

**( $\pm$ ) *Cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-6-(1-methylpiperidin-3-yl)methoxy)phenyl)acetamide**



25

**i) 2-Methyl-6-((1,1-dimethyl)-1-dimethylethyl)silyloxyaniline**

The subtitle compound was prepared from 2-amino-3-methylphenol (10g) and *tert*-butyldimethylsilyl chloride(12.22g) by the method of Example 97 step (i) as a brown oil.

Yield: 14g

5 <sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 6.53-6.70(m, 3H), 3.66(bs, 2H), 2.17(s, 3H), 1.02(s, 9H), 0.24(s, 6H)

**ii) 2-Chloro-N-(2-methyl-6-((1,1-dimethyl)-1-dimethylethyl)silyloxy)phenyl)acetamide**

The subtitle compound was prepared from the product of step (i) (5g) by the method of Example 111 step (ii) as pale yellow oil. Yield: 4.6g

10

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 7.97(bs, 1H), 7.07(t, 1H), 6.86(d, 1H), 6.72(d, 1H), 4.22(s, 2H), 2.23(s, 3H), 1.00(s, 9H), 0.22(s, 6H)

**iii) *Cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-6-((1,1-dimethyl)-1-dimethylethyl)silyloxy)phenyl)acetamide**

15

The subtitle compound was prepared from the product of step (ii) (1g) and the product of Example 80 step (ii) (0.89g) by the method of Example 80 step (iii) as a white solid.

This product was used directly in the next step

**iv) *Cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-6-hydroxy)phenyl)acetamide**

20

The subtitle compound was prepared from the product of step (iii) (2g) and tetra-butylammonium fluoride (3.18ml) by the method of Example 97 step (iv) as a white solid  
Yield: 0.8g

25

MS APCI(+ve) 441 (M-1)

**v) (±) *Cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-6-(1-methylpiperidin-3-yl)methoxy)phenyl)acetamide**

The title compound was prepared from the product of step (iv) (0.1 g) and ( $\pm$ ) 1-methyl-3-chloromethylpiperidine (76mg) by the method of Example 111 step (v) as a white solid.

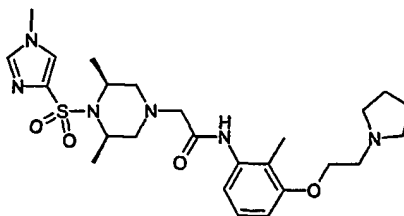
Yield: 26mg

5 MS: APCI(+ve) 540 (M+1)

$^1\text{H}$  NMR  $\delta$  ( $\text{CD}_3\text{OD}$ ) 8.29(s, 1H), 8.17(d, 1H), 7.98(d, 1H), 7.78(t, 1H), 7.17(t, 1H), 6.87(s, 1H), 6.84(s, 1H), 4.19-4.20(m, 2H), 3.83-3.88(m, 2H), 3.12(s, 2H), 2.80-3.0(m, 3H), 2.28(s, 3H), 2.20(s, 3H), 1.6-2.1(m, 9H), 1.55(d, 6H), 1.0-1.2(m, 1H)

#### 10 Example 117

***Cis-2-[4-(1-Methylimidazol-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-3-(2-(1-pyrrolidinyl)ethoxy)phenyl)acetamide***



i) ***Cis-1-(1-Methylimidazol-4-sulphonyl-4-yl)-2,6-dimethyl-4-phenylmethylpiperazine***

15 1-methylimidazol-4-sulphonyl chloride (19.45g) was added in small portions to a solution of *cis*-4-benzyl-2,6-dimethylpiperazine (20g) in pyridine (53ml) at 120 °C. After heating for a further 10min at reflux the solvent was evaporated under reduced pressure. The mixture was partitioned between dichloromethane and dilute sodium hydroxide solution. The organic phase collected, dried ( $\text{MgSO}_4$ ) and solvent evaporated under reduced  
20 pressure. Purification was by silica gel chromatography eluting with 0 to 5% methanol in dichloromethane to give the subtitle compound as pale yellow solid. Yield: 14.2g

$^1\text{H}$  NMR  $\delta$  ( $\text{CDCl}_3$ ) 7.22-7.46(m, 7H), 4.07-4.15(m, 2H), 3.73(s, 3H), 3.42(d, 2H), 2.53(d, 2H), 2.08(dd, 2H), 1.46(d, 6H)

25

ii) ***Cis-1-(1-Methylimidazol-4-sulphonyl-4-yl)-2,6-dimethylpiperazine***

The subtitle compound was prepared from the product of step (i) (14.07g) by the method of Example 80 step (ii) as tan solid. Yield: 12.16g

MS: APCI (+ve) 259(M+1)

5

**iii) *Cis*-2-[4-(1-Methylimidazol-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-3-((1,1-dimethyl)-1-dimethylethyl)silyloxy)phenyl)acetamide**

The subtitle compound was prepared from the product of step (ii) (0.82g) and the product of Example 111 step (ii) (1g) by the method of Example 80 step (iii) as a white solid.

10 Yield: 1.6g

<sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 8.83(s, 1H), 7.61(d, 1H), 7.47(s, 1H), 7.40(s, 1H), 7.07(t, 1H), 6.63(d, 1H), 4.21-4.24(m, 2H), 3.75(s, 3H), 3.10(s, 2H), 2.65(d, 2H), 2.17(s, 3H), 1.56(d, 6H), 1.02(s, 9H), 0.22(s, 6H)

15

**iv) *Cis*-2-[4-(1-Methylimidazol-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-3-hydroxy)phenyl)acetamide**

The subtitle compound was prepared from the product of step (iii) (1.51g) by the method of Example 111 step (iv) as a white solid. Yield: 0.4g

20

MS: APCI(+ve) 422 (M+1)

**v) *Cis*-2-[4-(1-Methylimidazol-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-3-(2-(1-pyrrolidinyl)ethoxy)phenyl)acetamide**

25 The title compound was prepared from the product of step (iv) (95mg) and 1-(2-chloroethyl)pyrrolidine (83mg) by the method of Example 111 step (v) as a white solid. Yield: 19mg

MS: APCI(+ve) 519 (M+1)



<sup>1</sup>H NMR  $\delta$  (CD<sub>3</sub>OD) 7.76(s, 1H), 7.67(s, 1H), 7.13-7.24(m, 2H), 6.84(d, 1H), 4.12-4.19(m, 4H), 3.78(s, 3H), 3.11(s, 2H), 3.01(t, 2H), 2.67-2.76(m, 6H), 2.18-2.28(m, 5H), 1.54(d, 6H)

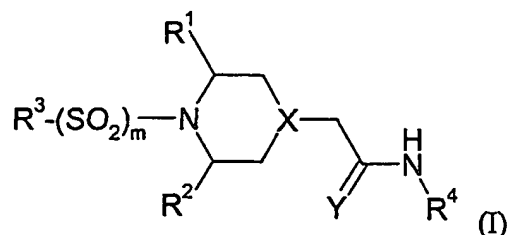
## 5 Pharmacological Analysis

Certain compounds such as benzoylbenzoyl adenosine triphosphate (bbATP) are known to be agonists of the P2X<sub>7</sub> receptor, effecting the formation of pores in the plasma membrane (Drug Development Research (1996), 37(3), p.126). Consequently, when the receptor is activated using bbATP in the presence of ethidium bromide (a fluorescent DNA  
10 probe), an increase in the fluorescence of intracellular DNA-bound ethidium bromide is observed. The increase in fluorescence can be used as a measure of P2X<sub>7</sub> receptor activation and therefore to quantify the effect of a compound on the P2X<sub>7</sub> receptor.

In this manner, each of the title compounds of the Examples was tested for antagonist  
15 activity at the P2X<sub>7</sub> receptor. Thus, the test was performed in 96-well flat bottomed microtitre plates, the wells being filled with 250  $\mu$ l of test solution comprising 200  $\mu$ l of a suspension of THP-1 cells ( $2.5 \times 10^6$  cells/ml) containing  $10^{-4}$ M ethidium bromide, 25  $\mu$ l of a high potassium buffer solution containing  $10^{-5}$ M bbATP, and 25  $\mu$ l of the high potassium buffer solution containing  $3 \times 10^{-5}$ M test compound. The plate was covered  
20 with a plastics sheet and incubated at 37 °C for one hour. The plate was then read in a Perkin-Elmer fluorescent plate reader, excitation 520 nm, emission 595 nm, slit widths: Ex 15 nm, Em 20 nm. For the purposes of comparison, bbATP (a P2X<sub>7</sub> receptor agonist) and pyridoxal 5-phosphate (a P2X<sub>7</sub> receptor antagonist) were used separately in the test as controls. From the readings obtained, a pIC<sub>50</sub> figure was calculated for each test  
25 compound, this figure being the negative logarithm of the concentration of test compound necessary to reduce the bbATP agonist activity by 50%. Each of the compounds of the Examples demonstrated antagonist activity, having a pIC<sub>50</sub> figure > 5.0.

## CLAIMS

1. A compound of general formula



5 wherein,

X represents a nitrogen atom or a group  $C(R^5)$ ;

Y represents an oxygen or sulphur atom or a group  $NR^6$ ;

either  $R^1$  and  $R^2$  each independently represent a hydrogen atom or a  $C_1$ - $C_4$  alkyl group but do not both simultaneously represent a hydrogen atom, or  $R^1$  and  $R^2$  together  
10 represent a group  $-CH_2ZCH_2-$ ;

Z represents a bond, an oxygen or sulphur atom or a group  $CH_2$  or  $NR^7$ ;

m is 0 or 1;

$R^3$  represents a 5- to 10-membered unsaturated ring system which may comprise  
from 1 to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur,  
15 the ring system being optionally substituted by one or more substituents independently  
selected from halogen, nitro, cyano,  $NR^8R^9$ ,  $C_1$ - $C_4$  alkyl- $C(O)NH-$ ,  $NHR^{12}C(O)-$ ,  
 $C_1$ - $C_4$  alkyl- $SO_2-$ ,  $C_1$ - $C_4$  alkyl- $SO_2NH-$ ,  $C_1$ - $C_4$  alkyl- $NHSO_2-$ ,  $C_1$ - $C_4$  alkoxy, and  
 $C_1$ - $C_4$  alkyl optionally substituted by one or more fluorine atoms;

$R^4$  represents a phenyl or pyridinyl group, each of which is substituted in an ortho  
20 position with a substituent selected from halogen,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  alkylthio, and  
 $C_1$ - $C_4$  alkyl optionally substituted by one or more fluorine atoms, the phenyl or pyridinyl  
group being optionally further substituted by one or more substituents independently  
selected from halogen, cyano, hydroxyl,  $C_1$ - $C_4$  alkylthio,  $C_1$ - $C_4$  alkyl- $NH-$ ,  
 $NHR^{13}-C_1$ - $C_4$  alkyl-,  $C_1$ - $C_4$  alkyl- $SO_2-$ ,  $C_1$ - $C_4$  alkyl- $SO_2NH-$ ,  
25  $C_1$ - $C_4$  alkyl- $NHSO_2-$ ,  $C_1$ - $C_4$  alkyl- $C(O)NH-$ ,  $C_1$ - $C_4$  alkyl- $NHC(O)-$ , -D-G,  
 $C_1$ - $C_4$  alkoxy optionally substituted by  $-NR^{14}R^{15}$  or by  $R^{16}$ , and

C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted by one or more fluorine atoms or by one or more hydroxyl groups,

or R<sup>4</sup> represents a 9- or 10-membered unsaturated bicyclic ring system which may comprise from 1 to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, the bicyclic ring system being optionally substituted by one or more substituents independently selected from halogen, oxo, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkylthio and -NR<sup>10</sup>R<sup>11</sup>;

D represents an oxygen atom or a group (CH<sub>2</sub>)<sub>n</sub> or CH<sub>2</sub>NH;

n is 1, 2 or 3;

G represents a piperazinyl, morpholinyl or 2,5-diazabicyclo[2.2.1]heptyl group, or G represents a piperidinyl group optionally substituted by amino;

R<sup>5</sup> represents a hydrogen atom, or a hydroxyl or C<sub>1</sub>-C<sub>4</sub> alkoxy group;

R<sup>6</sup> represents a hydrogen atom, or a cyano, nitro, hydroxyl, C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkoxy group;

R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> each independently represent a hydrogen atom or a C<sub>1</sub>-C<sub>4</sub> alkyl group;

R<sup>10</sup> and R<sup>11</sup> each independently represent a hydrogen atom or a C<sub>1</sub>-C<sub>4</sub> alkyl group, or R<sup>10</sup> and R<sup>11</sup> together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated heterocyclic ring comprising one or two ring nitrogen atoms;

R<sup>12</sup> represents a hydrogen atom, or a C<sub>1</sub>-C<sub>4</sub> alkyl group optionally substituted by amino;

R<sup>13</sup> represents a hydrogen atom, or a C<sub>1</sub>-C<sub>4</sub> alkyl group optionally substituted by hydroxyl;

R<sup>14</sup> and R<sup>15</sup> each independently represent a hydrogen atom or a C<sub>1</sub>-C<sub>4</sub> alkyl group optionally substituted by hydroxyl, or R<sup>14</sup> and R<sup>15</sup> together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated heterocyclic ring comprising one or two ring nitrogen atoms; and

R<sup>16</sup> represents a 1-(C<sub>1</sub>-C<sub>4</sub>-alkyl)-piperidinyl group;

with the proviso that when m is 0, X is N and Y is O, then R<sup>4</sup> does not represent 2-benzothiazolyl;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1, wherein X represents a nitrogen atom.
3. A compound according to claim 1 or claim 2, wherein Y represents an oxygen atom.

5

4. A compound according to any one of claims 1 to 3, wherein, in  $R^3$ , the 5- to 10-membered unsaturated ring system is selected from phenyl, pyridinyl, pyrimidinyl, naphthyl, furanyl, pyrrol, thienyl, isothiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, pyrazinyl, quinolinyl, isoquinolinyl, benzofuranyl, isobenzofuranyl, benzothienyl, pyrazolyl, indolyl, isoindolyl, purinyl, oxazolyl, isoxazolyl, thiazolyl, triazinyl, benzothiazolyl, benzooxazolyl, imidazopyrazinyl, triazolopyrazinyl, naphthyridinyl, furopyridinyl, thiopyranopyrimidinyl, pyridazinyl, quinazolinyl, pteridinyl, triazolopyrimidinyl, triazolopyrazinyl, thiapurinyl, oxapurinyl, deazapurinyl, thiazolopyrimidinyl, indolinyl, benzooxadiazolyl, benzothiadiazolyl, tetrahydroisoquiniliny, 2-(isoxazol-3-yl)thienyl, and thienopyrimidinyl.

5. A compound according to any one of the preceding claims, wherein, in  $R^3$ , the ring system is optionally substituted by one or more substituents independently selected from methyl, amino, cyano, methoxy, chloro, nitro,  $NH_2C(O)-$ ,  $CH_3C(O)NH-$ ,  $CH_3SO_2-$ ,  $CH_3SO_2NH-$  and  $NH_2CH_2CH_2NHC(O)-$ .

6. A compound according to any one of the preceding claims, wherein, in  $R^4$ , an ortho substituent in the phenyl or pyridinyl group is halogen or  $C_1-C_4$  alkyl optionally substituted by one or more fluorine atoms.

25

7. A compound according to any one of claims 1 to 5, wherein, in  $R^4$ , the 9- or 10-membered unsaturated bicyclic ring system is selected from naphthyl, benzimidazolyl, quinolinyl, indolinyl, isoquinolinyl, benzofuranyl, isobenzofuranyl, benzothienyl, indolyl, isoindolyl, benzthiazolyl, benzoxazolyl and quinazolinyl.

30

8. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as defined in claim 1 which is selected from:

(+)-N-(2,6-Dimethylphenyl)-2-(3-methyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)acetamide,

5 *cis*-[2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)]-N-(2,6-dimethylphenyl)acetamide,

(+)-2-[3-Methyl-4-(4-methylphenyl)piperazin-1-yl]-N-(2,6-dimethylphenyl)acetamide,

10 *cis*-N-[3-Hydroxymethyl-2-methylphenyl]-2-(3,5-dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)acetamide,

(R)-2-[4-(1-Methylimidazol-4-sulphonyl-4-yl)-3-ethylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide,

*cis*-2-[3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl]-N-(2-methylphenyl)acetamide,

15 *cis*-N-(2-Chlorophenyl)-2-[3,5-dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl]acetamide,

*cis*-N-(2-Chlorophenyl)-2-[3,5-dimethyl-4-(9-methyl-9H-purin-6-yl)piperazin-1-yl]acetamide,

20 *cis*-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(isoquinolin-5-yl)acetamide,

*cis*-2-(3,5-Dimethyl-4-thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(quinolin-5-yl)acetamide,

*cis*-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(2-methyl-5-methylsulphonamidophenyl)acetamide,

25 *cis*-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(2-trifluoromethylphenyl)acetamide,

*cis*-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(3-methylpyridin-2-yl)acetamide,

30 *cis*-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(isoquinolin-1-yl)acetamide,

*cis*-4-(4-Amino-5-cyanopyrimidin-2-yl)-3,5-dimethylpiperazin-1-yl)-N-(2-chlorophenyl)acetamide,

*cis*-2-(4-Benzenesulphonyl-3,5-dimethylpiperazin-1-yl)-N-(2-chlorophenyl)acetamide,

5       (+)-N-(2,6-Dimethylphenyl)-2-[(3-methyl-4-thiazolo(5,4-*d*)pyrimidin-7-yl)piperazin-1-yl]acetamide,

*cis*-N-(2-Chlorophenyl)-2-[(3,5-dimethyl-4-quinazolin-4-yl)piperazin-1-yl]acetamide,

10       N-(2-Chlorophenyl)-2-[(8-(thieno[2,3-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

N-(2-Methylphenyl)-2-[8-(9-methyl-9H-purin-6-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

2-[8-(9-Methyl-9H-purin-6-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(quinolin-5-yl)acetamide,

15       N-(Quinolin-5-yl)-2-[8-thiazolo[5,4-*d*]pyrimidin-7-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

N-(2-Methylphenyl)-2-[(8-thiazolo[5,4-*d*]pyrimidin-7-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

20       N-(2-Methyl-5-(methylsulphonyl)amidophenyl)-2-[8-(9-methyl-9H-purin-6-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

N-[2-Methyl-5-(methylsulphonyl)amidophenyl]-2-[(8-thiazolo[5,4-*d*]pyrimidin-7-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

N-[2-Methyl-5-(methylsulphonyl)amidophenyl]-2-[4-(thieno[2,3-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

25       *cis*-2-(3,5-Dimethyl-4-(thieno[2,3-*d*]pyrimidin-4-yl)piperazin-1-yl)-N-(2-methyl-5-(1-piperazinylmethyl)phenyl)acetamide, hydrochloride salt,

N-(2-Methylphenyl)-2-[(8-(thieno[2,3-*d*]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

30       N-[5-(Methanesulphonylamido-2-methylphenyl)-2-[8-(thieno[2,3-*d*]pyrimidin-4-yl)-8-azabicyclo[3.2.1]oct-3-yl]acetamide,

N-(2-Methyl-5-(1-piperazinylmethyl)phenyl)-2-[(8-(thieno[2,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

*cis*-N-(5-(2-Aminoethoxy)-2-methyl-phenyl)-2-(3,5-dimethyl-4-(thieno[2,3-d]pyrimidin-4-yl)piperazin-1-yl)acetamide, hydrochloride salt,

5 *cis*-N-(5-(2-(N-Methylamino)ethoxy)-2-methyl-phenyl)-2-(3,5-dimethyl-4-(thieno[2,3-d]pyrimidin-4-yl)piperazin-1-yl)acetamide, hydrochloride salt,

*cis*-N-(5-(2-(N-Methylamino)ethoxy)-2-methyl-phenyl)-2-(4-benzenesulphonyl)-3,5-dimethylpiperazin-1-yl)acetamide,

*cis*-N-[5-(2-Aminoethoxy)-2-methyl-phenyl)-2-(4-benzenesulphonyl)-3,5-dimethylpiperazin-1-yl]acetamide, hydrochloride salt,

10 N-(2-Oxo-2,3-dihydro-1H-indol-4-yl)-2-(8-thieno[2,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl)acetamide

N-(3-Fluoro-2-methyl-phenyl)-2-((8-quinazolin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl)acetamide,

15 N-(2-Methylphenyl)-2-[8-(benzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

N-(3-Fluoro-2-methylphenyl)-2-[8-(benzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

*cis*-N-(3-Fluoro-2-methyl-phenyl)-2-(4-benzenesulphonyl)-3,5-dimethylpiperazin-1-yl)acetamide,

20 N-(2-Methylphenyl)-2-[8-(3-cyanobenzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

2-[8-(3-Methoxybenzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide,

25 2-[8-(Benzo[1,2,5]oxadiazole-4-sulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide,

2-[8-(Benzo[1,2,5]thiadiazole-4-sulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide,

2-[8-(5-Chlorothiemo-2-yl)sulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide,

30

2-[8-(2-Chlorobenzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide,

2-[8-(5-Chloro-2-methoxybenzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide,

5 2-[8-(4-Acetylaminoethoxybenzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide,

N-(2-Methylphenyl)-2-[(8-(3-methylthieno[2,3-d]pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]acetamide,

10 *cis*-2-(3,5-Dimethyl-4-(thieno[2,3-d]pyrimidin-4-yl)piperazin-1-yl)-N-(1-methyl-1H-benzoimidazol-2-yl)acetamide,

*cis*-2-(3,5-Dimethyl-4-(thieno[2,3-d]pyrimidin-4-yl)piperazin-1-yl)-N-(2-methyl-5-(4-piperidinylloxy)phenyl)acetamide, hydrochloride salt,

*cis*-2-(3,5-Dimethyl-4-benzenesulphonyl)piperazin-1-yl)-N-(2-methyl-5-(4-piperidinylloxy)phenyl)acetamide,

15 *cis*-2-(3,5-Dimethyl-4-(quinazolin-4-yl)piperazin-1-yl)-N-(2-methyl-5-(4-piperidinylloxy)phenyl)acetamide,

*cis*-2-(3,5-Dimethyl-4-(4-quinazolinyl)piperazin-1-yl)-N-(2-methyl-5-(piperazin-4-yl-methyl)phenyl)acetamide,

20 *cis*-2-(3,5-Dimethyl-4-(4-quinazolinyl)piperazin-1-yl)-N-(2-methyl-5-(2-(N-methylamino)ethoxy)phenyl)acetamide,

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide,

*cis*-N-(2-Methylphenyl)-2-[4-(3-nitrobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-acetamide,

25 *cis*-2-[4-(3-Aminobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide,

*cis*-2-(3,5-Dimethyl-4-(3-cyanobenzenesulphonyl)piperazin-1-yl)-N-(quinolin-5-yl)acetamide,

30 *cis*-2-(3,5-Dimethyl-4-(4-cyanobenzenesulphonyl)piperazin-1-yl)-N-(quinolin-5-yl)acetamide,



*cis*-2-(4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl)-N-(3-fluoro-2-methylphenyl)acetamide,

*cis*-2-(4-(4-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl)-N-(3-fluoro-2-methylphenyl)acetamide,

5 *cis*-2-[4-(3-Acetylaminobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide,

*cis*-2-[4-(3-Aminocarbonylbenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide,

10 *cis*-2-[4-(3-Methanesulphonylaminobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide,

*cis*-2-[4-(2-Methanesulphonylbenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(3-methoxy-2-methylphenyl)acetamide,

*cis*-2-[4-(2-Methanesulphonylbenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(3-fluoro-2-methylphenyl)acetamide,

15 *cis*-2-[4-(1-Methylimidazol-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide,

*cis*-2-[4-(1-Methylimidazol-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-(3-methoxy-2-methylphenyl)acetamide,

20 *cis*-2-[4-(1-Methylimidazol-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-(3-fluoro-2-methylphenyl)acetamide,

*cis*-2-[4-(3-Methanesulphonylbenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-trifluoromethylphenyl)acetamide,

*cis*-2-[4-(2-Aminoethylaminocarbonylbenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide,

25 *cis*-2-[4-(1,1,2,2-Tetrahydroisoquinilin-7-sulphonyl-7-yl)-3,5-dimethylpiperazin-1-yl]-N-(2,6-dimethylphenyl)acetamide,

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2,6-dimethylphenyl)acetamide,

30 *cis*-2-[4-(4-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide,

*cis*-2-[4-(2-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2,6-dimethylphenyl)acetamide, hydrochloride salt,

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-chlorophenyl)acetamide,

5       2-[8-(Isquinolin-1-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide,

*cis*-2-[4-(4-Acetamidobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide,

10       *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-trifluoromethylphenyl)acetamide,

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-methanesulphonamidophenyl)acetamide,

2-[8-(4-Benzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide,

15       2-[8-(2-Benzenesulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide,

*cis*-2-[4-(1,2-Dimethylimidazol-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide,

20       *cis*-2-[4-(5-Chloro-1,3-dimethylpyrazole-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-(3-methoxy-2-methylphenyl)acetamide,

2-[8-(2-(Isoxazol-3-yl)thiophen-5-yl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide,

2-[8-(1,1,2,2-Tetrahydroisoquinilin-7-sulphonyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-N-(2-methylphenyl)acetamide,

25       *cis*-2-[4-(5-Chloro-1,3-dimethylpyrazole-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide,

*cis*-2-[4-(3,5-Dimethylisoxazole-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide,

30       *cis*-2-[4-(2-Methanesulphonylbenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide,

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(3-methoxy-2-methylphenyl)acetamide,

*cis*-2-[4-(4-Methanesulphonylbenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methylphenyl)acetamide,

5 *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(5-cyano-2-methylphenyl)acetamide,

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(5-acetamido-2-methylphenyl)acetamide,

10 (R)-2-[4-(4-Cyanobenzenesulphonyl)-3-methylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide,

(S)-2-[4-(4-Cyanobenzenesulphonyl)-3-methylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide,

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-methanesulphonylphenyl)acetamide,

15 *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-(4-amino-1-piperidinyl)methyl)phenyl]acetamide,

(R)-2-[4-(4-Methanesulphonylbenzenesulphonyl)-3-methylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide,

20 (R)-2-[4-(4-Acetamidobenzenesulphonyl)-3-methylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide,

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-(1-piperazinylmethyl)phenyl)acetamide,

*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-(4-piperidinylamino)methyl)phenyl)acetamide,

25 *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-(1-morpholinyl)methyl)phenyl)acetamide,

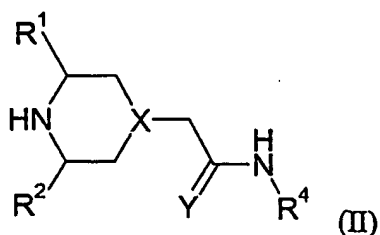
*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-(2-hydroxyethylamino)methyl)phenyl)acetamide,

30 *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-5-(S,S)-(2,5-diazabicyclo[2.2.1]hept-2-yl)methyl)phenyl)acetamide,

- (R)-2-[4-(2-Pyridinesulphonyl)-3-methylpiperazin-1-yl]-N-(quinolin-5-yl)acetamide,  
*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-3-(4-amino-1-piperidinyl)methyl)phenyl]acetamide,  
*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-3-(4-piperidinylamino)methyl)phenyl]acetamide,  
*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-3-(1-piperazinylmethyl)phenyl)acetamide,  
*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-(2-methyl-3-(S,S)-(2,5-diazabicyclo[2.2.1]hept-2-yl)methyl)phenyl)acetamide,  
*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-3-(1-morpholinyl)methyl)phenyl)acetamide,  
*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-3-(2-(1-pyrrolidinyl)ethoxy)phenyl)acetamide,  
 $(\pm)$  *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-3-(1-methylpiperidin-3-yl)methoxy)phenyl)acetamide,  
*cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-4-(2-(1-pyrrolidinyl)ethoxy)phenyl)acetamide,  
 $(\pm)$  *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-4-(1-methylpiperidin-3-yl)methoxy)phenyl)acetamide,  
 $(\pm)$  *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-5-(1-methylpiperidin-3-yl)methoxy)phenyl)acetamide,  
 $(\pm)$  *cis*-2-[4-(3-Cyanobenzenesulphonyl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-6-(1-methylpiperidin-3-yl)methoxy)phenyl)acetamide, and  
*cis*-2-[4-(1-Methylimidazol-4-sulphonyl-4-yl)-3,5-dimethylpiperazin-1-yl]-N-((2-methyl-3-(2-(1-pyrrolidinyl)ethoxy)phenyl)acetamide.

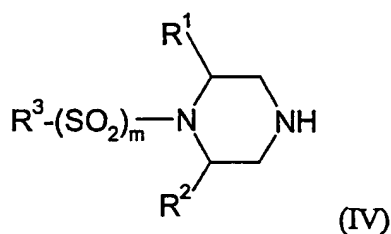
9. A process for the preparation of a compound of formula (I) as defined in claim 1, which comprises

(a) reacting a compound of general formula

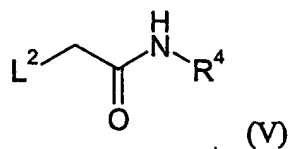


wherein X, Y, R<sup>1</sup>, R<sup>2</sup> and R<sup>4</sup> are as defined in formula (I), with a compound of general formula (III), R<sup>3</sup>-(SO<sub>2</sub>)<sub>m</sub>-L<sup>1</sup>, wherein L<sup>1</sup> represents a leaving group and m and R<sup>3</sup> are as defined in formula (I); or

- 5 (b) when X represents a nitrogen atom and Y represents an oxygen atom, reacting a compound of general formula

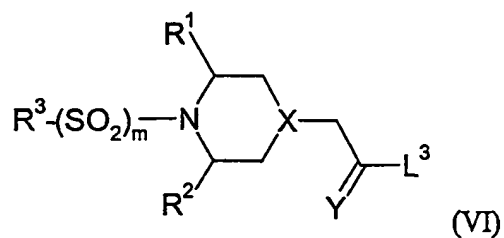


wherein m, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined in formula (I), with a compound of general  
10 formula



wherein L<sup>2</sup> represents a leaving group and R<sup>4</sup> is as defined in formula (I); or

- (c) reacting a compound of general formula



wherein  $L^3$  represents a leaving group and m, X, Y,  $R^1$ ,  $R^2$  and  $R^3$  are as defined in formula (I), with a compound of general formula (VII),  $H_2N - R^4$ , wherein  $R^4$  is as defined in formula (I);

5           and optionally after (a), (b) or (c) converting the compound of formula (I) obtained to a pharmaceutically acceptable salt or solvate thereof.

10.   A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8  
10   in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

11.   A process for the preparation of a pharmaceutical composition as claimed in claim 10 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined in any one of claims 1 to 8 with a pharmaceutically  
15   acceptable adjuvant, diluent or carrier.

12.   A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 for use in therapy.

20   13.   A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 for use in the treatment of rheumatoid arthritis.

14.   A compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 for use in the treatment of chronic obstructive  
25   pulmonary disease.

15.   Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 in the manufacture of a medicament for use in therapy.

16. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 in the manufacture of a medicament for use in treating rheumatoid arthritis.
- 5 17. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 in the manufacture of a medicament for use in treating chronic obstructive pulmonary disease.
- 10 18. A method of effecting immunosuppression which comprises administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 to a patient in need thereof.
- 15 19. A method of treating rheumatoid arthritis which comprises administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 to a patient in need thereof.
- 20 20. A method of treating chronic obstructive pulmonary disease which comprises administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 8 to a patient in need thereof.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 00/02580

## A. CLASSIFICATION OF SUBJECT MATTER

C07D 513/04, 495/04, 241/04, 473/34, 519/00, 403/04, A61K 31/496, 31/495

A61P 31/00, 37/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9931096 A1 (SHAMAN PHARMACEUTICALS, INC.), 24 June 1999 (24.06.99) --	1-20
X	EP 0582164 A1 (BRISTOL-MYERS SQUIBB COMPANY), 9 February 1994 (09.02.94) --	1-20
X	Chemical Abstracts, Volume 84, No 9, 1 March 1976, (01.03.76) (Columbus, Ohio, USA), page 527, THE ABSTRACT No 59466u, JP 75108264 A, (Maruyama, Isamuet al) 26 August 1975 (26.08.75) --	1-20



Further documents are listed in the continuation of Box C.



See patent family annex.

\*

Special categories of cited documents:

"A"

document defining the general state of the art which is not considered to be of particular relevance

"E"

earlier application or patent but published on or after the international filing date

"L"

document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O"

document referring to an oral disclosure, use, exhibition or other means

"P"

document published prior to the international filing date but later than the priority date claimed

"Γ"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;"

document member of the same patent family

Date of the actual completion of the international search

20 March 2001

Date of mailing of the international search report

30 -03- 2001

Name and mailing address of the ISA:

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 00/02580

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstracts, Volume 57 (1962), (Columbus, Ohio, USA), Shin Hayao et al, "New sedative and hypotensive phenylpiperazine amides", THE ABSTRACT No 3443i, J. Org. Chem. 1961, 26, 3414-3419 --	1-15
X	EP 0074768 A2 (RECORDATI S.A.), 23 March 1983 (23.03.83) --	1-20
X	US 3029241 A (OTIS E. FANCHER ET AL), 10 April 1962 (10.04.62), column 2, line 55 - line 64 --	1-15
X	FR 2346011 A1 (SOUCHARD MADDY), 28 October 1977 (28.10.77) --	1-20
X	WO 9959582 A1 (CENTAUR PHARMACEUTICALS, INC.), 25 November 1999 (25.11.99), page 12, line 19 - line 20, claims 29-31 --	1-20
X	STN International, File CAPLUS, CAPLUS accession no. 1995:324637, Document no. 122:105919, Kyowa Hakko Kogyo KK: Preparation of quinazolinylpiperazineacetamide derivatives"; & JP, A2, 06247942, 19940906 --	1-20
X	STN International, File CAPLUS, CAPLUS accession no. 1991:656226, Document no. 115:256226, Kowa K.K., "Preparation of piperazine derivatives as antiarrhythmics", & JP, A2, 19910617 -- -----	1-20

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE00/02580

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 18-20  
because they relate to subject matter not required to be searched by this Authority, namely:  
see next sheet
2. ☒ Claims Nos.: 1  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
Claim 1 is too broadly formulated to permit a meaningful search.  
Therefore, the search has mainly been restricted to the examples, i.e claim 8. See PCT, Article 6.

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims: it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE00/02580

Claims 18-20 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions:

## INTERNATIONAL SEARCH REPORT

Information on patent family members

25/02/01

International application No.

PCT/SE 00/02580

Patent document cited in search report			Publication date	Patent family member(s)	Publication date
WO	9931096	A1	24/06/99	AU 1924099 A	05/07/99
EP	0582164	A1	09/02/94	SE 0582164 T3	
				AT 174913 T	15/01/99
				AU 670953 B	08/08/96
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				CA 2101311 A	01/02/94
				CN 1085216 A	13/04/94
				DE 69322707 D,T	19/08/99
				DK 582164 T	23/08/99
				ES 2125285 T	01/03/99
				FI 933398 A	01/02/94
				GR 3029778 T	30/06/99
				HU 67460 A	28/04/95
				IL 106490 D	00/00/00
				JP 6157472 A	03/06/94
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				DE 3232672 A	21/04/83
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				ES 8503346 A	01/06/85
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				AU 3985699 A	06/12/99
				US 6113293 A	05/09/00
				WO 9961322 A	02/12/99